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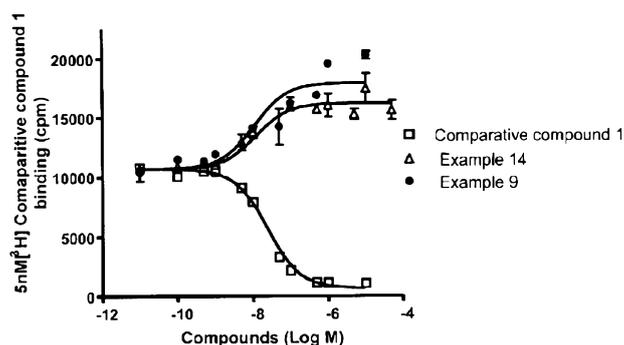
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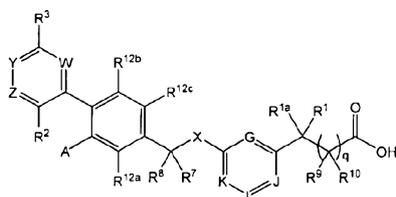
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(54) Title: SUBSTITUTED BIPHENYL GPR40 MODULATORS

Figure 1



(57) Abstract: The present invention provides compounds useful, for example, for treating metabolic disorders in a subject. Such compounds have the general formula I: where the definitions of the variables are provided herein. The present invention also provides compositions that include, and methods for using, the compounds in preparing medicaments and for treating metabolic disorders such as, for example, type II diabetes.



(I)



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SUBSTITUTED BIPHENYL GPR40 MODULATORS**1. CROSS REFERENCES TO RELATED APPLICATIONS**

[001] This application claims the benefit of United States Provisional Application No. 5 60/998,786, filed on October 10, 2007, and United States Provisional Application No. 61/068,724, filed on March 6, 2008, both of which are hereby incorporated by reference in their entireties and for all purposes as if specifically and fully set forth herein.

2. FIELD OF THE INVENTION

[002] The present invention relates to compounds capable of modulating the 10 G-protein-coupled receptor GPR40 and/or stimulating GLP-1 secretion, compositions comprising the compounds, and methods for their use for controlling insulin levels in vivo and for the treatment of conditions such as type II diabetes, hypertension, ketoacidosis, obesity, glucose intolerance, and hypercholesterolemia and related disorders associated with abnormally high or low plasma lipoprotein, triglyceride or glucose levels.

15 3. BACKGROUND OF THE INVENTION

[002a] Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

[003] The production of insulin is central to the regulation of carbohydrate and lipid 20 metabolism. Insulin imbalances lead to conditions such as type II diabetes mellitus, a serious metabolic disease that afflicts around 5% of the population in Western Societies and over 150 million people worldwide. Insulin is secreted from pancreatic β cells in response to elevated plasma glucose which is augmented by the presence of fatty acids. The recent recognition of the function of the G-protein coupled receptor GPR40 in modulating insulin secretion has provided 25 insight into regulation of carbohydrate and lipid metabolism in vertebrates, and further provided targets for the development of therapeutic agents for disorders such as obesity, diabetes, cardiovascular disease and dyslipidemia.

[004] GPR40 is a member of the gene superfamily of G-protein coupled receptors 30 ("GPCRs"). GPCRs are membrane proteins characterized as having seven putative transmembrane domains that respond to a variety of molecules by activating intra-cellular signaling pathways critical to a diversity of physiological functions. GPR40 was first identified as an orphan receptor (i.e., a receptor without a known ligand) from a human genomic DNA fragment. Sawzdargo et al. (1997) Biochem. Biophys. Res. Commun. 239: 543-547. GPR40 is highly expressed in pancreatic β cells and insulin-

secreting cell lines. GPR40 activation is linked to modulation of the G_q family of intracellular signaling proteins and concomitant induction of elevated calcium levels. It has been recognized that fatty acids serve as ligands for GPR40, and that fatty acids regulate insulin secretion through GPR40. Itoh et al. (2003) *Nature* 422:173-176; Briscoe et al. (2003) *J. Biol. Chem.* 278: 11303-11311; Kotarsky et al. (2003) *Biochem. Biophys. Res. Commun.* 301: 406-410.

[005] Various documents have disclosed compounds reportedly having activity with respect to GPR40. For example, WO 2004/041266 and EP 1559422 disclose compounds that purportedly act as GPR40 receptor function regulators. WO 2004/106276 and EP 1630152 are directed to condensed ring compounds that purportedly possess GPR40 receptor function modulating action. More recently, WO 2005/086661 U.S. Patent Publication No. 2006/0004012, US Patent Publication No. 2006/0270724, and US Patent Publication No. 2007/0066647 disclose compounds useful for modulating insulin levels in subjects and useful for treating type II diabetes.

[006] Although a number of compounds have been disclosed that reportedly modulate GPR40 activity, the prevalence of type II diabetes, obesity, hypertension, cardiovascular disease and dyslipidemia underscores the need for new therapies to effectively treat or prevent these conditions.

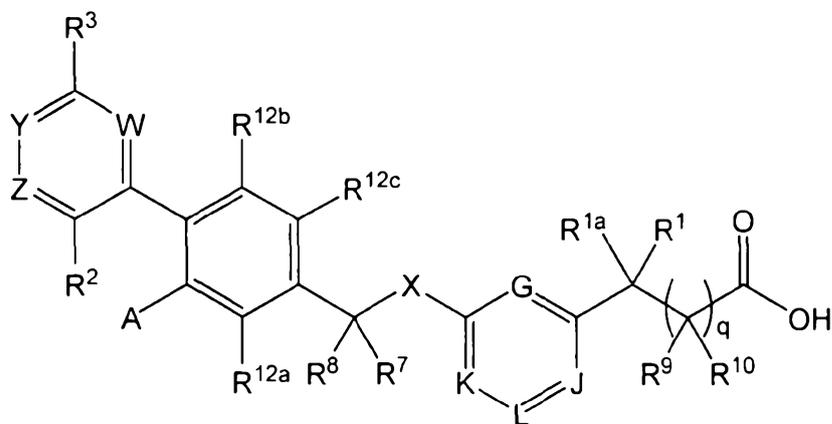
[007] Glucagon-like peptide 1 (GLP-1) is a peptide that is secreted from the enteroendocrine L-cells of the gut in response to an oral glucose load or food ingestion. The active forms of GLP-1 are processed from a precursor and are denoted GLP-1(7-37) and GLP-1(7-36) amide. GLP-1 has many effects on peripheral tissues. GLP-1 activates its cognate receptor GLP-1R (GLP-1 receptor) on pancreatic beta cells and potentiates glucose stimulated insulin secretion. Additionally, GLP-1 decreases glucagon levels, increases insulin biosynthesis, increases beta cell mass, decreases beta cell apoptosis and inhibits gastric emptying. These activities contribute to an improvement in hyperglycemia, and GLP-1 and GLP-1 mimetics have proven useful in the treatment of type 2 diabetes. GLP-1 has also been found to decrease body weight. Therefore, GLP-1 secretagogues may be useful in treating obesity and preparing medicaments for treating obesity. The decrease in body weight may result from the activities of GLP-1 to inhibit gastric emptying and to increase satiety. The GLP-1 receptor is also expressed in the heart and GLP-1 has been demonstrated to have cardioprotective effects and may be useful in the treatment of cardiovascular disease. The importance of GLP-1 with respect

to diabetes, obesity and cardioprotection underscores a need for new therapies and compounds that stimulate GLP-1 secretion.

4. SUMMARY OF THE INVENTION

5 [005] Provided herein are compounds, pharmaceutical compositions, and methods useful for treating a condition or disorder such as type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic
10 disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer or edema.

[006] In a first aspect, the present invention provides a compound of formula I:



I

15 or a pharmaceutically acceptable salt, stereoisomer, C₁-C₆ alkyl ester, or mixture thereof wherein

G is selected from N or CR^{11a};

J is selected from N or CR^{11b};

L is selected from N or CR^{11c};

20 K is selected from N or CR^{11d};

wherein 0 or 1 of G, J, L, and K is N;

A is selected from -(C₁-C₁₂)alkyl; -(C₂-C₁₂)alkenyl; -(C₁-C₁₂)alkyl-O-(C₁-C₄)alkyl; -(C₁-C₁₂)alkyl-OH; -(C₁-C₁₂)alkyl-O-(C₂-C₄)alkenyl; -(C₂-C₁₂)alkenyl-O-(C₁ _____

C_4 alkyl; $-(C_2-C_{12})$ alkenyl-OH; $-(C_2-C_{12})$ alkenyl-O- (C_2-C_4) alkenyl; -O- (C_1-C_{12}) alkyl;
 -O- (C_2-C_{12}) alkenyl; -O- (C_1-C_4) alkyl-aryl; -S- (C_1-C_{12}) alkyl; -S- (C_2-C_{12}) alkenyl;
 -S(O)- (C_1-C_{12}) alkyl; -S(O)- (C_2-C_{12}) alkenyl; -S(O)₂- (C_1-C_{12}) alkyl; -S(O)₂- (C_2-C_{12}) alkenyl;
 a heterocycle comprising 4 to 7 ring members of which 1 or 2 are heteroatoms selected
 from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members
 and is unsubstituted or is substituted with from 1 to 4 (C_1-C_2) alkyl groups; a $-(C_1-$
 $C_4)$ alkyl-heterocyclyl wherein the heterocyclyl of the $-(C_1-C_4)$ alkyl-heterocyclyl
 comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S
 wherein the heterocycle has 0 or 1 double bond between ring members and is
 unsubstituted or is substituted with from 1 to 4 (C_1-C_2) alkyl groups; or a -O-heterocyclyl
 wherein the heterocyclyl of the -O-heterocyclyl comprises 4 to 7 ring members of which
 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double
 bond between ring members and is unsubstituted or is substituted with from 1 to 4 $(C_1-$
 $C_2)$ alkyl groups; further wherein the alkyl and alkenyl groups of $-(C_1-C_{12})$ alkyl, $-(C_2-$
 $C_{12})$ alkenyl, $-(C_1-C_{12})$ alkyl-O- (C_1-C_4) alkyl, $-(C_1-C_{12})$ alkyl-O-H, $-(C_1-C_{12})$ alkyl-O- $(C_2-$
 $C_4)$ alkenyl, $-(C_2-C_{12})$ alkenyl-O- (C_1-C_4) alkyl, $-(C_2-C_{12})$ alkenyl-OH, $-(C_2-C_{12})$ alkenyl-O-
 (C_2-C_4) alkenyl, -O- (C_1-C_{12}) alkyl, -O- (C_2-C_{12}) alkenyl, and -O- (C_1-C_4) alkyl-aryl are
 unsubstituted or are substituted with from 1 to 4 substituents selected from -F, -Cl, -OH,
 (=O), -NH₂, NH (C_1-C_4) alkyl, -N $((C_1-C_4)$ alkyl)₂, aryl, unsubstituted $-(C_1-C_2)$ alkyl, or
 unsubstituted -O- (C_1-C_2) alkyl;

X is O, S, or NR^a wherein R^a is selected from -H or $-(C_1-C_6)$ alkyl groups;

W, Y, and Z are selected from N or CR¹³; wherein 0, 1, or 2 of W, Y, and Z is N;

and further wherein Z is not N if R² is -F;

R¹ is selected from -H, $-(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkenyl, $-(C_2-C_6)$ alkynyl, $-(C_1-$
 $C_4)$ alkyl-O- (C_1-C_4) alkyl, heterocyclyl, aryl, or heteroaryl;

R^{1a} is selected from -H and $-(C_1-C_4)$ alkyl;

or R¹ and R^{1a} may join together to form a 3 to 7 membered ring with 0, 1, or 2
 heteroatoms selected from O, N, or S ;

R² is selected from -H, -F, -CF₃, or -O- (C_1-C_6) alkyl;

R³ is -H, -F, -Cl, -OH, $-(C_1-C_4)$ alkyl, -O- (C_1-C_3) alkyl, or -S- (C_1-C_2) alkyl;

R⁷ and R⁸ are independently selected from -H and $-(C_1-C_4)$ alkyl;

R⁹ and R¹⁰ are independently selected from -H and $-(C_1-C_4)$ alkyl;

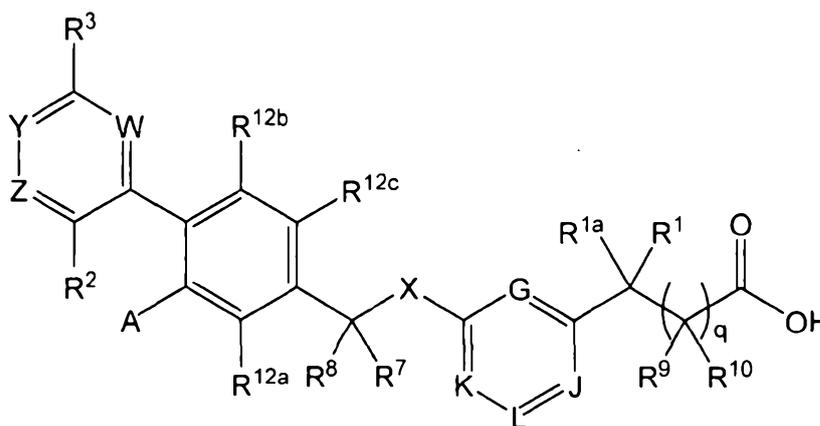
each of R^{11a} , R^{11b} , R^{11c} , and R^{11d} is independently selected from -H, -F, -Cl, -(C₁-C₄)alkyl, or -O-(C₁-C₄)alkyl; and R^{11a} is absent if G is N; R^{11b} is absent if J is N, R^{11c} is absent if L is N; or R^{11d} is absent if K is N;

each of R^{12a} , R^{12b} , and R^{12c} is independently selected from -H, -F, -Cl, -(C₁-C₄)alkyl, or -O-(C₁-C₄)alkyl;

R^{13} is selected from -H, -F, -(C₁-C₄)alkyl, and -O-(C₁-C₄)alkyl; and

q is 1 or 2.

[009a] In a second aspect, the present invention provides a compound of formula I:



I

or a pharmaceutically acceptable salt, stereoisomer, C₁-C₆ alkyl ester, or a mixture thereof, wherein

G is selected from N or CR^{11a};

J is selected from N or CR^{11b};

L is selected from N or CR^{11c};

K is selected from N or CR^{11d};

wherein 0 or 1 of G, J, L, and K is N;

A is selected from (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, -O-(C₁-C₁₂)alkyl, -O-(C₂-C₁₂)alkenyl, -O-(C₁-C₄)alkyl-aryl, or a heterocycle comprising 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N or O, wherein the heterocycle has 0 or 1 double bond between ring members;

X is O or S;

W, Y, and Z are selected from N or CR¹³; wherein 0 or 1 of W, Y, and Z is N; and further wherein Z is not N if R² is F;

R¹ is selected from H, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -(C₁-C₄)alkyl-O-(C₁-C₄)alkyl, heterocyclyl, aryl, or heteroaryl;

R^{1a} is selected from H and (C₁-C₄)alkyl;

R² is selected from H, F, CF₃, or (C₁-C₆)alkoxy;

R^3 is H, -OH, -O-(C₁-C₂)alkyl, or -S-(C₁-C₂)alkyl;

R^7 and R^8 are independently selected from H and (C₁-C₄)alkyl;

R^9 and R^{10} are independently selected from H and (C₁-C₄)alkyl;

Each of R^{11a} , R^{11b} , R^{11c} , and R^{11d} is independently selected from H, F, Cl, (C₁-C₄)alkyl,
5 or (C₁-C₄)alkoxy; and R^{11a} is absent if G is N; R^{11b} is absent if J is N, R^{11c} is absent if L is N; or
 R^{11d} is absent if K is N;

Each of R^{12a} , R^{12b} , and R^{12c} is independently selected from H, F, Cl, (C₁-C₄)alkyl, or (C₁-
C₄)alkoxy;

R^{13} is selected from H, F, (C₁-C₄)alkyl, and -O-(C₁-C₄)alkyl; and
10 q is 1 or 2.

[009b] In a third aspect, the present invention provides a pharmaceutical composition, comprising: a pharmaceutically acceptable carrier, diluent, or excipient, and the compound of any one of Claims 1-43.

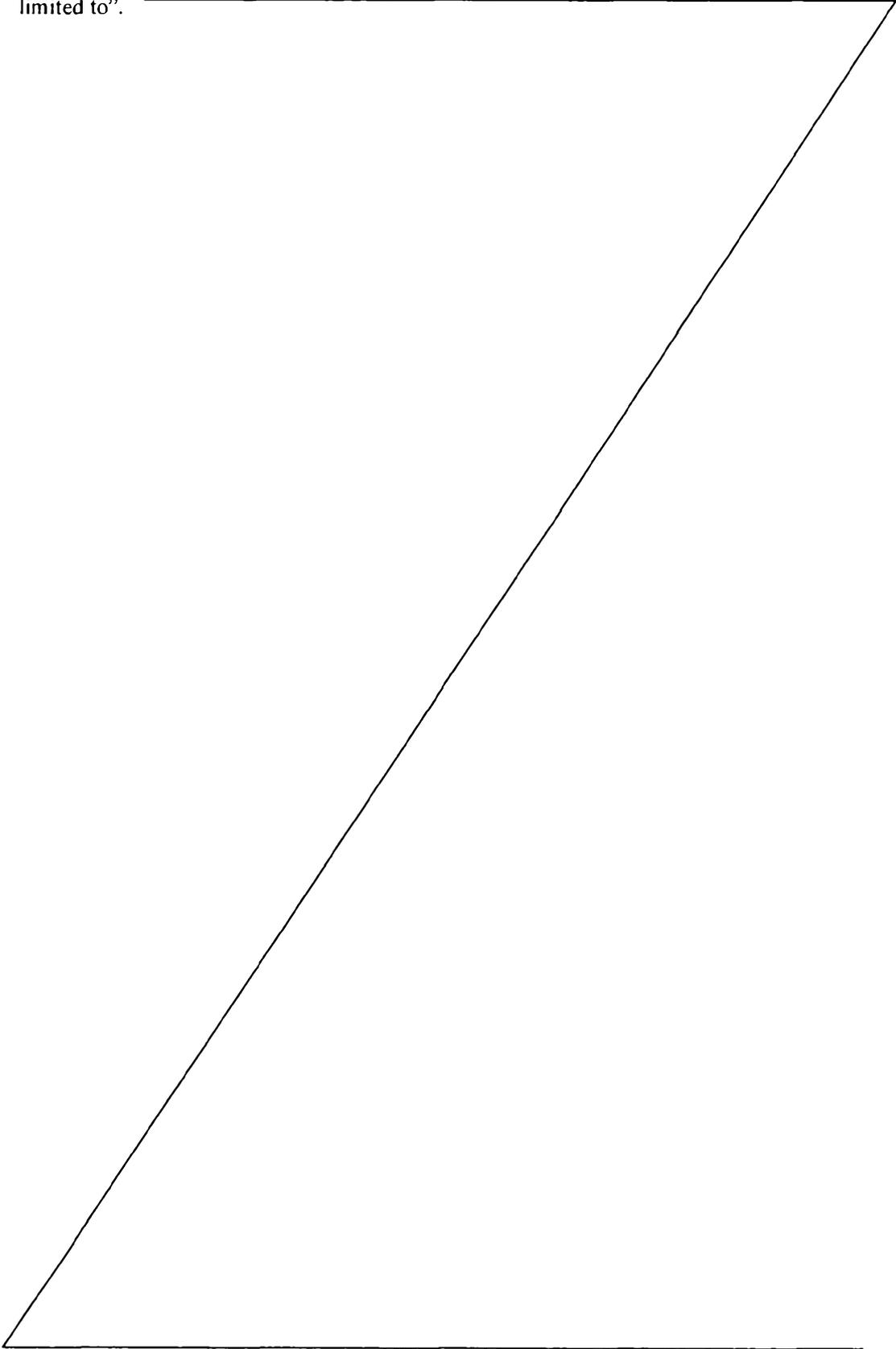
[009c] In a fourth aspect, the present invention provides the use of the compound of the
15 invention in the preparation of a medicament for treating a disease or condition selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders,
20 nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema.

[009d] In a fifth aspect, the present invention provides the use of the compound of the invention in the preparation of a medicament for increasing GLP-1 levels in the blood plasma of a subject.

[009e] In a sixth aspect, the present invention provides a method for treating a disease
25 or condition, comprising: administering to a subject in need thereof, a therapeutically effective amount of the compound of the invention, wherein the disease or condition is selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia,
30 hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer, and edema.

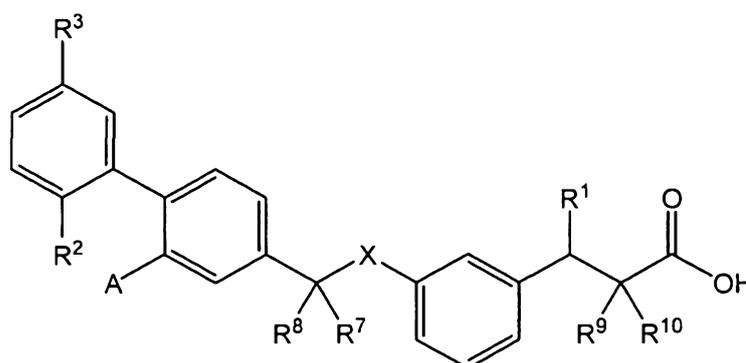
[009f] Unless the context clearly requires otherwise, throughout the description and the claims,
35 the words "comprise", "comprising", and the like are to be construed in an inclusive sense as

opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".



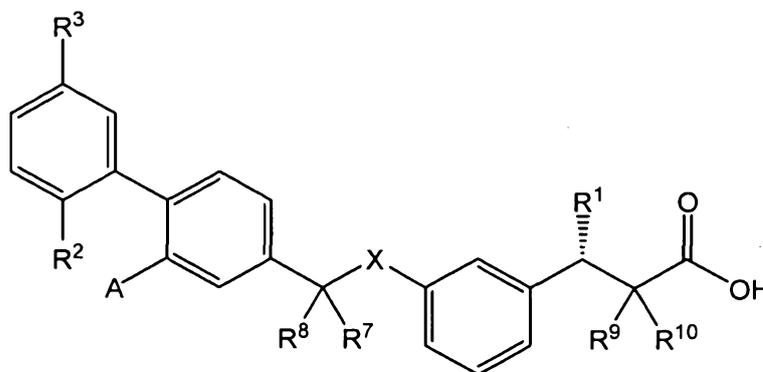
R^{13} is selected from H, F, (C_1-C_4) alkyl, and $-O-(C_1-C_4)$ alkyl; and q is 1 or 2.

[011] In some embodiments, X is O. In other embodiments, X is S. In still further embodiments X is NR^a . In some embodiments X is NR^a and R^a is selected from H or methyl. In still other embodiments, X is NR^a and R^a is H. In some embodiments, the compound of formula I is a compound of formula II or a pharmaceutically acceptable salt, stereoisomer, C_1-C_6 alkyl ester, or mixture thereof. The compound of formula II has the following structure where each of the variables has any of the values of any of the embodiments described herein:



II.

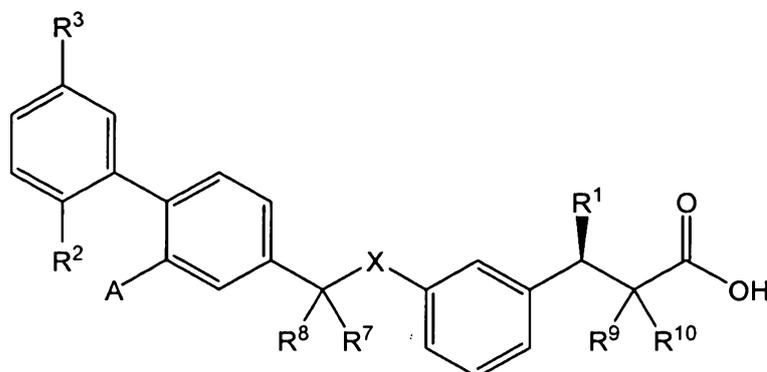
[012] In some embodiments, the compound of formula II is a compound of formula II' or a pharmaceutically acceptable salt, stereoisomer, C_1-C_6 alkyl ester, or mixture thereof. The compound of formula II' has the following structure where each of the variables has any of the values of any of the embodiments described herein:



II'.

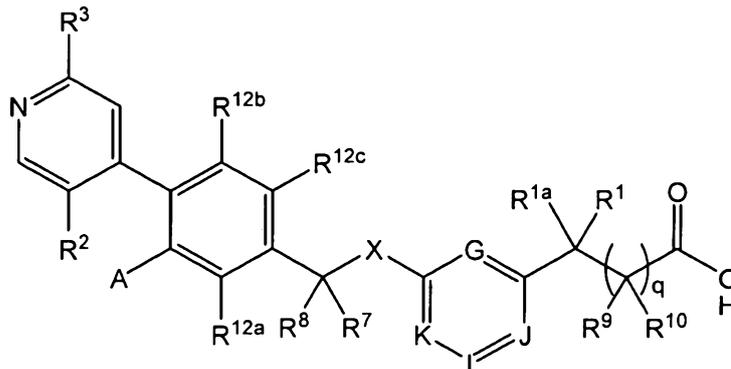
[013] In some embodiments, the compound of formula II is a compound of formula II'' or a pharmaceutically acceptable salt, stereoisomer, C_1-C_6 alkyl ester, or

mixture thereof. The compound of formula **II'** has the following structure where each of the variables has any of the values of any of the embodiments described herein:



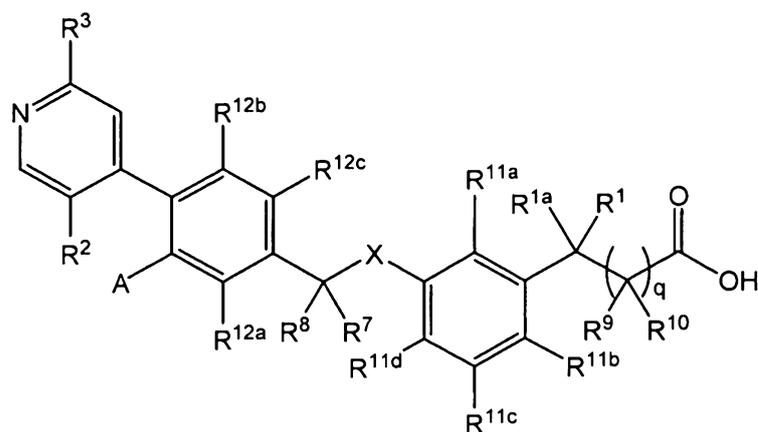
II'.

[014] In some embodiments of the compound of formula **I**, W and Z are CH and Y is N such that the compound of formula **I** has the formula **III** or is a pharmaceutically acceptable salt, stereoisomer, C₁-C₆ alkyl ester, or mixture thereof. The compound of formula **III** has the following structure where each of the variables has any of the values of any of the embodiments described herein:



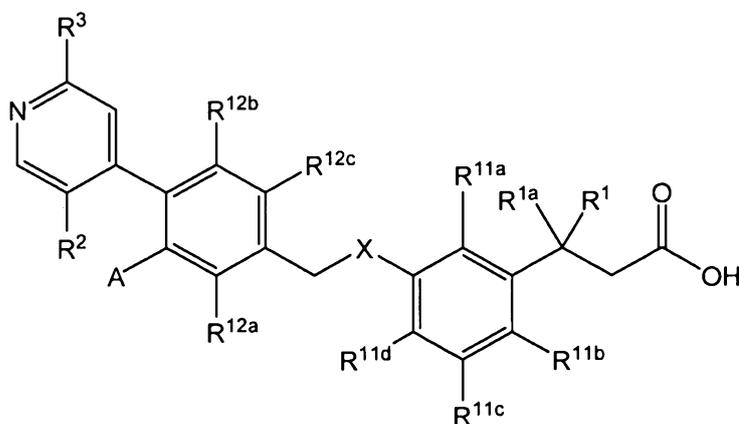
III.

[015] In some embodiments, the compound of formula **III** is a compound of formula **III'** or a pharmaceutically acceptable salt, stereoisomer, C₁-C₆ alkyl ester, or mixture thereof. The compound of formula **III'** has the following structure where each of the variables has any of the values of any of the embodiments described herein:



III'.

[016] In some embodiments, the compound of formula III is a compound of formula III'' or a pharmaceutically acceptable salt, stereoisomer, C₁-C₆ alkyl ester, or mixture thereof. The compound of formula III'' has the following structure where each of the variables has any of the values of any of the embodiments described herein:



III''.

[017] In some embodiments, the compound of any of the embodiments is a salt. In other embodiments, the compound of any of the embodiments is a C₁-C₆ alkyl ester. In some such embodiments, the C₁-C₆ alkyl ester is a C₁-C₆ alkyl ester such as a methyl, ethyl, propyl, butyl, isopropyl, pentyl, or hexyl ester. In other such embodiments, the C₁-C₆ alkyl ester is a methyl, ethyl, propyl, or butyl ester. In some such embodiments, the ester is a methyl or ethyl ester.

[018] In some embodiments, where two or more chiral centers are present, the compound is a mixture of diastereomers. In some such embodiments, the percentage of one diastereomer is greater than 75%, greater than 80%, greater than 85%, greater than

90%, greater than 95%, greater than 98%, or greater than 99% based on the total diastereomers present in the mixture. In other embodiments, the compound is one specific diastereomer. In some embodiments, the compound is a mixture of enantiomers. In some such embodiments, the mixture comprises both enantiomers where the percent of one enantiomer with respect to both enantiomers is greater than 75%, greater than 80%, greater than 85%, greater than 90%, greater than 95%, greater than 98%, or greater than 99%. In other embodiments, the compound is a pure single enantiomer. In some embodiments with a single chiral center, the compound comprises a stereomerically pure S-enantiomer. In other embodiments with a single chiral center, the compound comprises a stereomerically pure R-enantiomer. In yet other embodiments with a single chiral center, the compound comprises a mixture of S- and R-enantiomers.

[019] In another aspect, the invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier, diluent, or excipient, and a compound of any of the embodiments of the invention.

[020] In another aspect, the invention provides methods for treating a disease or condition selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer, and edema. Such methods include administering to a subject in need thereof, a therapeutically effective amount of a compound of any of the embodiments. In some such embodiments, the disease or condition is type II diabetes. In some embodiments, a compound of any of the embodiments is administered in combination with a second therapeutic agent. In some such embodiments, the second therapeutic agent is metformin, is a thiazolidinedione, is a DPP-IV inhibitor or is a GLP-1 analog. The second therapeutic agent may be administered before, during, or after administration of the compound of any of the embodiments.

[021] In another aspect, the invention provides methods for treating a disease or condition responsive to the modulation of GPR40. Such methods include administering to a subject in need thereof, a therapeutically effective amount of a compound of any of the embodiments.

[022] In another aspect, the invention provides methods for treating a disease or condition mediated, regulated, or influenced by pancreatic β cells. Such methods include administering to a subject in need thereof, a therapeutically effective amount of a compound of any of the embodiments.

[023] In another aspect, the invention provides methods for modulating GPR40 function in a cell. Such methods include contacting a cell with a compound of any of the embodiments.

[024] In another aspect, the invention provides methods for modulating GPR40 function. Such methods include contacting GPR40 with a compound of any of the embodiments.

[025] In another aspect, the invention provides methods for modulating circulating insulin concentration in a subject. Such methods include administering a compound of any of the embodiments to the subject. In some such embodiments, the circulating insulin concentration is increased in the subject after administration whereas in other such embodiments, the circulating insulin concentration is decreased in the subject after administration.

[026] In another aspect, the invention provides the use of a compound of any of the embodiments for treating a disease or condition or for preparing a medicament for treating a disease or condition where the disease or condition is selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer, and edema. In some such embodiments, the disease or condition is type II diabetes. The compounds of the invention may also be used to prepare medicaments that include a second therapeutic agent such as metformin, a thiazolidinedione, or a DPP-IV inhibitor.

[027] In another aspect, the invention provides the use of a compound of any of the embodiments for modulating GPR40 or for use in the preparation of a medicament for modulating GPR40.

[028] In another aspect, the invention provides a therapeutic composition that includes a compound of any of the embodiments and a second therapeutic agent such as

those described herein, for example, metformin a thiazolidinedione, or a DPP-IV inhibitor, as a combined preparation for simultaneous, separate, or sequential use in the treatment of a disease or condition mediated by GPR40. In some such embodiments, the disease or condition is type II diabetes. In some embodiments, the compound of any of the embodiments and the second therapeutic agent are provided as a single composition, whereas in other embodiments they are provided separately as parts of a kit.

[029] In some embodiments, the invention provides a compound of any of the embodiments described herein for use as a medicament.

[030] In other embodiments, the invention provides a compound of any of the embodiments described herein for use in modulating GPR40.

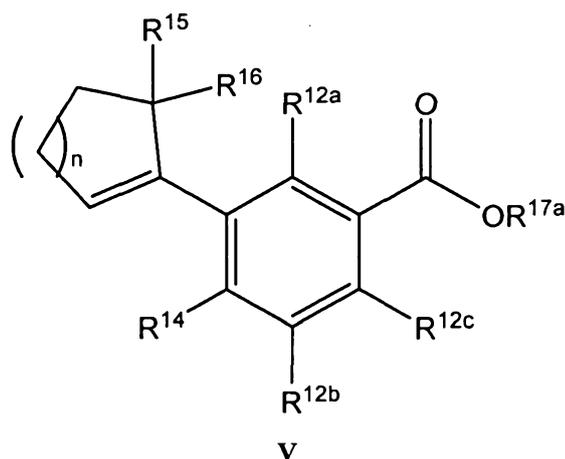
[031] In still other embodiments, the invention provides a compound of any of the embodiments described herein for use in a method for treating a disease or condition selected from type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer, or edema.

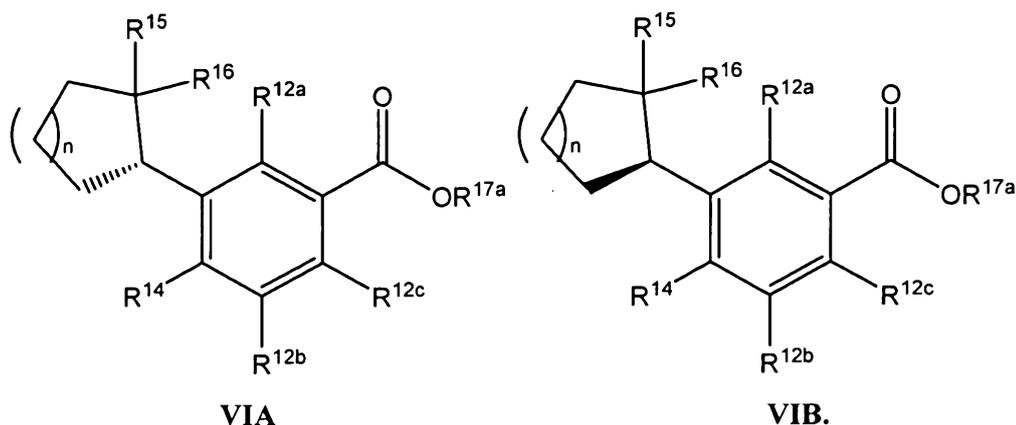
[032] The compounds of the invention have been found to stimulate GLP-1 secretion. Cells contacted with compounds of the invention have been found to increase GLP-1 secretion. Therefore, in some embodiments, the invention provides a method of stimulating GLP-1 secretion by cells. Such methods typically include contacting a cell capable of producing GLP-1 with a compound of any of the embodiments set forth herein. Administration of the compounds of the invention to subjects has also been found to provide increased levels of GLP-1 in the blood plasma of such subjects. Therefore, in some embodiments, a compound of any of the embodiments described herein may be used to stimulate GLP-1 secretion and increase the blood plasma level of GLP-1 in a subject. In some such embodiments, the compounds of the invention both stimulate GLP-1 secretion and activate GPR40. Therefore, in some embodiments, the compounds of the invention both stimulate GLP-1 secretion and display incretin effect by activating GPR40.

[033] In some embodiments, the invention further provides a method for increasing GLP-1 levels in the blood plasma of a subject. Such methods typically include administering a compound of any of the embodiments to a subject. In some such embodiments, the subject is a diabetic patient. In other such embodiments, the subject is

an obese patient. In some embodiments, the invention provides a method for stimulating weight loss in a subject. In such embodiments, a compound of any of the embodiments is administered to a subject in an effective amount to stimulate weight loss in the subject. The compounds of the invention may be administered in the fasted or non-fasted state. Therefore, in some embodiments, a compound of any of the embodiments is administered to a subject prior to a meal. In some such embodiments, the compound is administered 2 hours, 1 hour, 30 minutes, or 15 minutes before a meal. In other embodiments, a compound of any of the embodiments set forth herein is administered to a subject during a meal. In other embodiments, a compound of any of the embodiments described herein is administered to a subject within 2 hours, within 1 hour, within 30 minutes, or within 15 minutes of a meal.

[034] In another aspect the invention provide a process for hydrogenating a compound of formula **V**, the method comprising: (a) reacting a compound of formula **V** with H_2 in the presence of a transition metal or a transition metal complex to form a compound of formula **VIA**, a compound of formula **VIB** or mixture of the compound of formula **VIA** and the compound of formula **VIB**. The compounds of formula **V**, **VIA**, and **VIB** have the following structures:





wherein,

R^{12a} is selected from -H, halo, a $-(C_1-C_6)$ alkyl group, or a $-O-(C_1-C_6)$ alkyl group;

R^{12b} is selected from -H, halo, a $-(C_1-C_6)$ alkyl group, or a $-O-(C_1-C_6)$ alkyl group;

R^{12c} is selected from -H, halo, a $-(C_1-C_6)$ alkyl group, or a $-O-(C_1-C_6)$ alkyl group;

R^{14} is -H or -OH;

R^{15} is selected from -H, or a $-(C_1-C_6)$ alkyl group;

R^{16} is selected from -H, or a $-(C_1-C_6)$ alkyl group;

R^{17a} is a $-(C_1-C_6)$ alkyl group; and

the subscript n is 1, 2, or 3;

wherein at least one of R^{15} or R^{16} is a $-(C_1-C_6)$ alkyl group.

[035] In another aspect, the invention provides a compound of formula V, VIA, and/or VIB. In such an aspect, the variables have the definitions provided herein with respect to the process for hydrogenating a compound of formula V. In various embodiments of this aspect, the variables have any of the definitions provided with respect to any of the embodiments of the process for hydrogenating a compound of formula V. For example, in some embodiments, R^{14} is OH. In other such embodiments, R^{15} and R^{16} are both methyl groups.

[036] In some embodiments of the process for hydrogenating the compound of formula V, the transition metal or transition metal complex comprises palladium, platinum, nickel, or rhodium. For example, the reduction may be accomplished using palladium on carbon, Raney nickel, PtO_2 or various rhodium compounds. In some such embodiments, the transition metal or transition metal complex is palladium, and in some such embodiments is palladium on carbon. Various supported catalysts known to those skilled in the art may be used in conjunction with this process.

[037] In some embodiments of the process for hydrogenating the compound of formula **V**, the process is an enantioselective process. In such embodiments, the method includes reacting a compound of formula **V** with H₂ in the presence of a transition metal or a transition metal complex and a phosphine ligand to form a compound of formula **VIA**, a compound of formula **VIB**, or a mixture of the compound of formula **VIA** and the compound of formula **VIB**. In such embodiments, the phosphine ligand comprises at least one chiral center.

[038] In some embodiments of the process for hydrogenating a compound of formula **V**, R¹⁴ is -OH.

[039] In some embodiments of the process for hydrogenating a compound of formula **V**, R¹⁵ and R¹⁶ are both -CH₃.

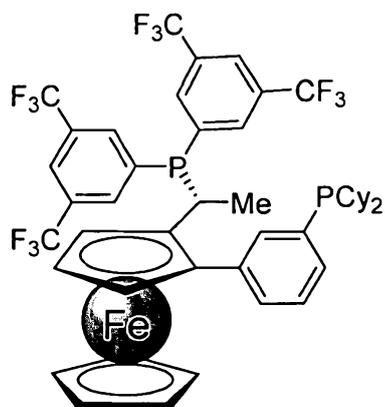
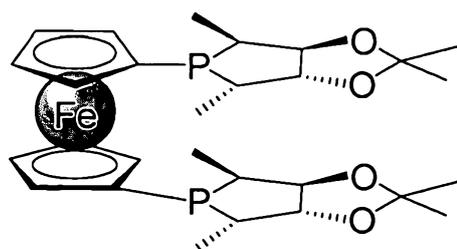
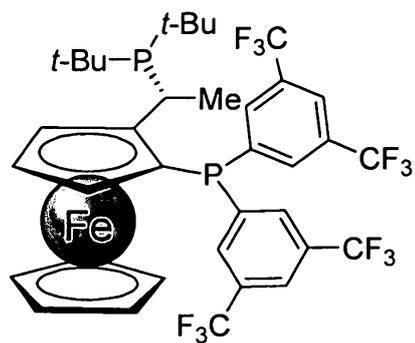
[040] In some embodiments of the process for hydrogenating a compound of formula **V**, the subscript n is 1.

[041] In some embodiments of the process for hydrogenating a compound of formula **V**, R^{12b} and R^{12c} are both -H.

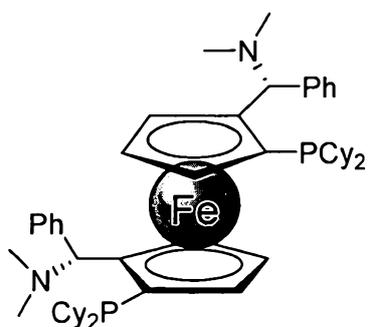
[042] In some embodiments of the process for hydrogenating a compound of formula **V**, R^{12a} is H or halo. Thus, in some embodiments R^{12a} is H whereas in other embodiments, R^{12a} is F.

[043] In some embodiments of the process for hydrogenating a compound of formula **V**, the transition metal or the transition metal complex comprises rhodium. For example, in some such embodiments, the transition metal complex is generated from Rh(COD)₂BF₄, Rh(COD)₂SbF₆, or Rh(NBD)₂BF₄ where COD represents the 1,5-cyclooctadiene ligand and NBD represents the norbornadiene ligand.

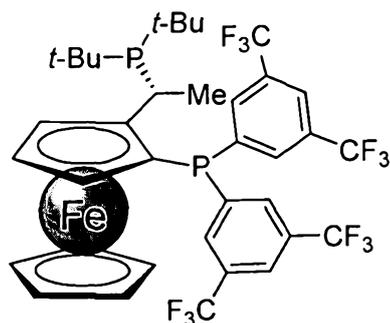
[044] In some embodiments of the process for hydrogenating a compound of formula **V**, the phosphine is a diphosphine. In some such embodiments, the diphosphine comprises a ferrocene group. In some such embodiments, the diphosphine is selected from



, or



In some such embodiments, the diphosphine is



In other such embodiments, the diphosphine is an enantiomer of one of the compounds shown above.

[045] In some embodiments of the process for hydrogenating a compound of formula V, the compound of formula V is reacted with H₂ at a pressure of from 15 to 1400 psi. In some such embodiments, the pressure ranges from 50 to 400 psi.

[046] In some embodiments of the process for hydrogenating a compound of formula V, the compound of formula V is reacted with H₂ in a mixture comprising at least one solvent selected from an ethereal solvent, an ester solvent, an aromatic solvent, a halogenated hydrocarbon solvent, a ketone solvent, or a C₁-C₄ alcohol solvent. In some such embodiments, the at least one solvent comprises an ethereal solvent selected from tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, 1,2-diethoxyethane, tetrahydropyran, diethylether, dipropylether, or dibutylether. In other such embodiments, the at least one solvent comprises tetrahydrofuran. In other such embodiments, the at least one solvent comprises at least one of tetrahydrofuran, toluene, acetone, methyl ethyl ketone, ethanol, or methanol.

[047] In some embodiments, the transition metal complex is mixed with the phosphine in a solvent prior to adding the compounds of formula V. In some such embodiments, the solvent is an ethereal solvent such as tetrahydrofuran, and the transition metal complex is selected from Rh(COD)₂BF₄, Rh(COD)₂SbF₆, or Rh(NBD)₂BF₄. In some such embodiments, the phosphine is a diphosphine comprising a ferrocenyl group such as one of those described herein.

[048] In some embodiments of the process for hydrogenating a compound of formula V, the compound of formula I is reacted with H₂ at a temperature ranging from 15°C to 60°C. In some such embodiments, the temperature ranges from 20°C to 45°C.

[049] In some embodiments of the process for hydrogenating a compound of formula V, the enantiomeric excess of one of the products is greater than 50%, greater

than 60%, greater than 75%, greater than 85%, greater than 90%, greater than 95%, or greater than 98%.

[050] In some embodiments of the process for hydrogenating a compound of formula V, the conversion of the compound of formula V to the compound of formula VIA, the compound of formula VIB, or the mixture of the compound of formula VIA and the compound of formula VIB is greater than 50%, greater than 70%, greater than 80%, or greater than 95%.

[051] Other objects, features and advantages of the invention will become apparent to those skilled in the art from the following description and claims.

5. BRIEF DESCRIPTION OF THE DRAWINGS

[052] Figure 1 is a graph showing displacement of ³H-labeled Comparative Compound 1 by various unlabeled compounds, including Examples 9 and 14. Unlabeled Comparative Compound 1 displaced the ³H-labeled Comparative Compound. In direct contrast, Examples 9 and 14 enhanced the total binding of ³H-labeled Comparative Compound 1. These results indicate that Examples 9 and 14 interact with the GPR40 receptor in a manner that is different from Comparative Compound 1.

[053] Figure 2 is a graph showing Aequorin luminescence in response to various compounds as a function of concentration. This graph shows that Examples 14 and 66.4 have activity which is equivalent to naturally occurring fatty acid ligands such as α -linolenic acid and docosahexaenoic acid.

[054] Figure 3 is a graph showing inositol phosphate accumulation in response to various compounds as a function of concentration. This graph shows that Examples 9 and 14 have activity which is greater than Comparative Compound 1.

[055] Figure 4 is a graph showing insulin secretion from C57/B16 mouse islets as a function of concentration of Examples 9 and 14.

[056] Figure 5 is a graph showing the concentration of GLP-1 secreted into culture medium as a function of the amount of Example compounds 14 and 69.8. The GLP-1 was secreted from fetal rat intestinal cells isolated from E19 rat embryos. The cultured cells were treated with serial dilutions of the indicated compounds, and GLP-1 secreted into the culture medium was determined. These results indicate that these compounds significantly stimulated GLP-1 secretion.

[057] Figure 6 is a graph showing the concentration of GLP-1 secreted into culture medium as a function of the amount of Example compound 66.6. The GLP-1 was secreted from fetal rat intestinal cells isolated from E19 rat embryos. The cultured cells were treated with serial dilutions of the indicated compound, and GLP-1 secreted into the culture medium was determined. These results indicate that this compound significantly stimulated GLP-1 secretion.

[058] Figure 7 is a graph showing the concentration of GLP-1 secreted into culture medium as a function of the amount of Example compounds 14, 66.17, 77.3, and 83.1. The GLP-1 was secreted from fetal rat intestinal cells isolated from E19 rat embryos. The cultured cells were treated with serial dilutions of the indicated compounds, and GLP-1 secreted into the culture medium was determined. These results indicate that these compounds significantly stimulated GLP-1 secretion.

[059] Figure 8 is a graph showing GLP-1 plasma levels in C57BL6 mice under overnight fast condition after administration of vehicle and Example 14 (100 mg/kg). Each group had 12 mice. The * symbol indicates that for this point $p < 0.05$ (student's t-test) when treatment with example compound is compared with vehicle control. Only the top part of the error bars is shown.

[060] Figure 9 is a graph showing GLP-1 plasma levels in C57BL6 mice under non-fasted condition after administration of vehicle and Example 14 (100 mg/kg). Each group had 12 mice. The * symbol indicates that for this point $p < 0.05$ (student's t-test) when treatment with example compound is compared with vehicle control. Only the top part of the error bars is shown.

[061] Figure 10 is a graph showing GLP-1 plasma levels in HF/STZ mice under non-fasted condition after administration of vehicle and Example 14 (100 mg/kg). Each group had 12 mice. The * symbol indicates that for this point $p < 0.05$ (student's t-test) when treatment with example compound is compared with vehicle control. Only the top part of the error bars is shown.

[062] Figure 11 is a graph showing GLP-1 plasma levels in HF/STZ mice under non-fasted condition after administration of vehicle and Example 83.1 (30 mg/kg). Each group had 12 mice. The * symbol indicates that for this point $p < 0.05$ (student's t-test) when treatment with example compound is compared with vehicle control. Only the top part of the error bars is shown.

6. DETAILED DESCRIPTION OF THE INVENTION

6.1 Abbreviations and Definitions

[063] The terms “treat”, “treating” and “treatment”, as used herein, are meant to include alleviating or abrogating a condition or disease and/or its attendant symptoms. In some instances treating may also involve prevention of symptoms. The terms “prevent”, “preventing” and “prevention”, as used herein, refer to a method of delaying or precluding the onset of a condition or disease and/or its attendant symptoms, barring a subject from acquiring a condition or disease, or reducing a subject’s risk of acquiring a condition or disease.

[064] The term “therapeutically effective amount” refers to that amount of the compound that will elicit the biological or medical response of a tissue, system, or subject that is being sought. The term “therapeutically effective amount” includes that amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the condition or disorder being treated in a subject. The therapeutically effective amount in a subject will vary depending on the compound, the disease and its severity, and the age, weight, etc., of the subject to be treated.

[065] The term “subject” is defined herein to include animals such as mammals, including, but not limited to, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice and the like. In preferred embodiments, the subject is a human.

[066] The terms “modulate”, “modulation” and the like refer to the ability of a compound to increase or decrease the function or activity of GPR40 either directly or indirectly. Inhibitors are compounds that, for example, bind to, partially or totally block stimulation, decrease, prevent, delay activation, inactivate, desensitize, or down regulate signal transduction, such as, for instance, antagonists. Activators are compounds that, for example, bind to, stimulate, increase, activate, facilitate, enhance activation, sensitize or up regulate signal transduction, such as agonists for instance. Modulation may occur in vitro or in vivo.

[067] As used herein, the phrases “GPR40-mediated condition or disorder”, “disease or condition mediated by GPR40”, and the like refer to a condition or disorder characterized by inappropriate, for example, less than or greater than normal, GPR40 activity. A GPR40-mediated condition or disorder may be completely or partially

mediated by inappropriate GPR40 activity. However, a GPR40-mediated condition or disorder is one in which modulation of GPR40 results in some effect on the underlying condition or disease (e.g., a GPR40 modulator results in some improvement in patient well-being in at least some patients). Exemplary GPR40-mediated conditions and disorders include cancer and metabolic disorders, e.g., diabetes, type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, ketoacidosis, hypoglycemia, thrombotic disorders, metabolic syndrome, syndrome X and related disorders, e.g., cardiovascular disease, atherosclerosis, kidney disease, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, and edema.

[068] The term “alkyl”, by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which is fully saturated, having the number of carbon atoms designated (e.g., C₁-C₁₀ means one to ten carbons). Examples of alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, pentyl, cyclohexyl, (cyclohexyl)methyl, methylcyclohexyl, dimethylcyclohexyl, cyclopropyl, cyclopropylmethyl, methylcyclopropyl, cyclobutyl, cyclobutylmethyl, methylcyclobutyl, cyclopentyl, methylcyclopentyl, cyclopentylmethyl, dimethylcyclopentyl, and homologs and isomers thereof, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. Alkyl groups may be substituted or unsubstituted.

[069] The term “alkenyl”, by itself or as part of another substituent, means a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be mono- or polyunsaturated, having the number of carbon atoms designated (i.e., C₂-C₈ means two to eight carbons) and one or more double bonds. Examples of alkenyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), cyclopentenyl, cyclohexenyl, 5,5-dimethylcyclopentenyl, 6,6-dimethylcyclohexenyl, cycloheptenyl, cycloheptadienyl, and higher homologs and isomers thereof.

[070] The term “alkynyl”, by itself or as part of another substituent, means a straight or branched chain hydrocarbon radical, or combination thereof, which may be mono- or polyunsaturated, having the number of carbon atoms designated (i.e., C₂-C₈ means two to eight carbons) and one or more triple bonds. Examples of alkynyl groups

include, but are not limited to, ethynyl, 1- and 3-propynyl, 3-butynyl, and higher homologs and isomers thereof.

[071] The term “alkoxy” refers to a group of formula –O-alkyl where alkyl has the definition provided above. An alkoxy group can have a specified number of carbon atoms. For example, a methoxy group (–OCH₃) is a C₁ alkoxy group. Alkoxy groups typically have from 1 to 10 carbon atoms. Examples of alkoxy group include, but are not limited to, methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, heptoxy, and the like.

[072] The term “cycloalkyl” by itself, or in combination with other terms, represents, unless otherwise stated, a cyclic type of “alkyl” in which 3 or more carbon atoms form a ring. Thus, the term “cycloalkyl” is meant to be included in the term “alkyl”. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like. Cycloalkyl groups typically include from 3 to 14 or 3 to 10 ring members. Cycloalkyl groups may be monocyclic, bicyclic, or multicyclic. Therefore, in addition to the groups described above, cycloalkyl groups include norbornyl and adamantyl groups.

[073] The term “cycloalkenyl” by itself, or in combination with other terms, represents, unless otherwise stated, a cyclic type of “alkenyl” in which 3 or more carbon atoms form a ring that includes at least one carbon-carbon double bond. Thus, the term “cycloalkenyl” is meant to be included in the term “alkenyl”. Examples of cycloalkenyl include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. Cycloalkenyl groups typically include from 3 to 14 or 3 to 10 ring members. Cycloalkenyl groups may be monocyclic, bicyclic, or multicyclic.

[074] The term “heterocyclyl” by itself or in combination with other terms, represents, unless otherwise stated, a ring system in which one or more ring members is a heteroatom selected from N, O, or S. The heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. A heterocyclyl group can also be attached to the remainder of the molecule through a carbon atom of the ring. Heterocyclyl groups typically include from 3 to 10 ring members of which 1, 2, or 3 are heteroatoms. Heterocyclyl groups can be saturated or may include some unsaturation. Heterocyclyl groups may also be substituted or unsubstituted. Examples of heterocyclyl groups include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, 4,5-dihydroisoxazol-3-yl, and the like.

[075] The term “heteroalkyl,” by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any position of the heteroalkyl group. Examples include $-\text{CH}_2\text{-CH}_2\text{-O-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-NH-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-N(CH}_3\text{)-CH}_3$, $-\text{CH}_2\text{-S-CH}_2\text{-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-S(O)-CH}_3$, $-\text{CH}_2\text{-CH}_2\text{-S(O)}_2\text{-CH}_3$, and $-\text{CH}_2\text{-CH=N-OCH}_3$. Up to two heteroatoms may be consecutive, such as, for example, $-\text{CH}_2\text{-NH-OCH}_3$. When a prefix such as $(\text{C}_2\text{-C}_8)$ is used to refer to a heteroalkyl group, the number of carbons (2 to 8, in this example) is meant to include the heteroatoms as well. For example, a C_2 -heteroalkyl group is meant to include, for example, $-\text{CH}_2\text{OH}$ (one carbon atom and one heteroatom replacing a carbon atom) and $-\text{CH}_2\text{SH}$.

[076] To further illustrate the definition of a heteroalkyl group, where the heteroatom is oxygen, a heteroalkyl group is a oxyalkyl group. For instance, $(\text{C}_2\text{-C}_5)$ oxyalkyl is meant to include, for example $-\text{CH}_2\text{-O-CH}_3$ (a C_3 -oxyalkyl group with two carbon atoms and one oxygen replacing a carbon atom), $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, and the like.

[077] The terms “halo” or “halogen,” by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as “haloalkyl”, are meant to include alkyl substituted with halogen atoms which can be the same or different, in a number ranging from one to $(2m' + 1)$, where m' is the total number of carbon atoms in the alkyl group. For example, the term “halo $(\text{C}_1\text{-C}_4)$ alkyl” is meant to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like. Thus, the term “haloalkyl” includes monohaloalkyl (alkyl substituted with one halogen atom) and polyhaloalkyl (alkyl substituted with halogen atoms in a number ranging from two to $(2m' + 1)$ halogen atoms). The term “perhaloalkyl” means, unless otherwise stated, alkyl substituted with $(2m' + 1)$ halogen atoms, where m' is the total number of carbon atoms in the alkyl group. For example, the term “perhalo $(\text{C}_1\text{-C}_4)$ alkyl”, is meant to include trifluoromethyl, pentachloroethyl, 1,1,1-trifluoro-2-bromo-2-chloroethyl, and the like.

[078] The term “aryl” means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. The term “heteroaryl” refers to aryl

groups (or rings) that contain from one to four heteroatom ring members selected from the group consisting of N, O and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. Heteroaryl groups can be unsubstituted or substituted. In some embodiments, a heteroaryl group includes 1 or 2 heteroatoms. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom or through a carbon atom of the ring. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-pyrazolyl, 3-pyrazolyl, 5-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, dibenzofuryl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 5-benzothiazolyl, 2-benzoxazolyl, 5-benzoxazolyl, benzo[c][1,2,5]oxadiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1H-indazolyl, carbazolyl, α -carbolinyl, β -carbolinyl, γ -carbolinyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalyl, 5-quinoxalyl, 2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, and 8-quinolyl. Typically an aryl group refers to an aromatic group that includes from 6-10 ring members such that it is a (C₆-C₁₀)aryl group. Typically, heteroaryl groups include 5 to 10 ring members of which 1 or 2 is selected from O, N, or S.

[079] Preferably, the term "aryl" refers to a phenyl or naphthyl group which is unsubstituted or substituted. Preferably, the term "heteroaryl" refers to a pyrrolyl, pyrazolyl, imidazolyl, pyrazinyl, oxazolyl, oxadiazolyl, isoxazolyl, thiazolyl, furyl, thienyl (thiophenyl), pyridyl, pyrimidyl, benzothiazolyl, purinyl, benzimidazolyl, indolyl, isoquinolyl, triazolyl, tetrazolyl, quinoxalyl, or quinolyl group which is unsubstituted or substituted.

[080] For brevity, the term "aryl" when used in combination with other terms (e.g., aryloxy, arylalkoxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (e.g., benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (e.g., a methylene group) has been replaced by, for example, an oxygen atom (e.g., phenoxyethyl, 2-pyridyloxyethyl, 3-(1-naphthoxy)propyl, and the like). As another example, the term "aryl(C₁-C₄)alkoxy" is meant to include radicals in which an aryl group is attached to an alkyl group having 1 to 4 carbon atoms that is bonded to an O which is attached to the rest

of the molecule. Examples include substituted and unsubstituted phenylmethoxy, phenylethoxy, phenylpropoxy, pyridylmethoxy, and the like.

[081] Each of the above terms (e.g., “alkyl,” “alkenyl,” “aryl,” “heterocyclyl” and “heteroaryl”) is meant to include both substituted and unsubstituted forms of the indicated radical, unless otherwise indicated. Preferred substituents for each type of radical are provided below.

[082] Substituents for the alkyl radicals (as well as those groups referred to as alkenyl, alkynyl, cycloalkyl, and heterocyclyl) can be a variety of groups selected from: -OR', =O, =NR', =N-OR', -NR'R'', R', -SR', halogen, -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR'-SO₂NR''R''', -NR''CO₂R', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -SiR'R''R''', -S(O)R', -SO₂R', -SO₂NR'R'', -NR''SO₂R', -CN, -(C₂-C₅) alkynyl, -(C₂-C₅) alkenyl, and -NO₂, in a number ranging from zero to three, with those groups having zero, one or two substituents being particularly preferred. R', R'' and R''' each independently refer to hydrogen; unsubstituted (C₁-C₈)alkyl, (C₂-C₈)alkenyl, and heteroalkyl; unsubstituted aryl; unsubstituted heterocyclyl; heterocyclyl substituted with up to three unsubstituted (C₁-C₂)alkyl groups; aryl substituted with one to three halogens, unsubstituted (C₁-C₂)alkyl, -O-(C₁-C₄)alkyl, and -S-(C₁-C₄)alkyl groups; unsubstituted halo(C₁-C₄)alkyl; unsubstituted -(C₁-C₄)alkyl-O-(C₁-C₄)alkyl; unsubstituted -(C₁-C₄)alkyl-aryl; or unsubstituted aryl-(C₁-C₄)alkyl groups. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6- or 7-membered ring. For example, -NR'R'' is meant to include 1-pyrrolidinyl and 4-morpholinyl.

[083] Typically, an alkyl group will have from zero to three substituents, with those groups having two or fewer substituents being preferred in the present invention. More preferably, an alkyl radical will be unsubstituted or monosubstituted. Most preferably, an alkyl radical will be unsubstituted. From the above discussion of substituents, one of skill in the art will understand that the term “alkyl” is meant to include groups such as trihaloalkyl (e.g., -CF₃ and -CH₂CF₃).

[084] Preferred substituents for the alkyl radicals are selected from: -OR', =O, -NR'R'', -SR', halogen, -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR''CO₂R', -NR'-SO₂NR''R''', -S(O)R', -SO₂R', -SO₂NR'R'', -NR''SO₂R', -CN, -(C₂-C₅) alkynyl, -(C₂-C₅) alkenyl, R', and -NO₂, where R' and R'' are as defined above. Further preferred substituents are selected from: -OR', =O, -NR'R'', halogen, -

OC(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR''CO₂R', -NR'-SO₂NR''R''', -SO₂R', -SO₂NR'R'', -NR''SO₂R, -CN, -(C₂-C₅) alkynyl, -(C₂-C₅) alkenyl, and -NO₂.

[085] Similarly, substituents for the aryl and heteroaryl groups are varied and are selected from: -halogen, -OR', -OC(O)R', -NR'R'', -SR', -R', -CN, -NO₂, -CO₂R', -CONR'R'', -C(O)R', -OC(O)NR'R'', -NR''C(O)R', -NR''C(O)₂R', -NR'-C(O)NR''R''', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -N₃, -CH(Ph)₂, perfluoro(C₁-C₄)alkoxy, and perfluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R'' and R''' are independently selected from hydrogen, unsubstituted (C₁-C₈)alkyl and heteroalkyl; unsubstituted aryl and heteroaryl; unsubstituted aryl-(C₁-C₄)alkyl; unsubstituted aryl-O-(C₁-C₄)alkyl; unsubstituted -(C₂-C₅)alkynyl; and unsubstituted -(C₂-C₅) alkenyl.

[086] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CH₂)_q-U-, wherein T and U are independently -NH-, -O-, -CH₂-, or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CH₂-, -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'-, or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -(CH₂)_s-X-(CH₂)_t-, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR'-. The substituent R' in -NR'- and -S(O)₂NR'- is selected from hydrogen or unsubstituted (C₁-C₆)alkyl. Otherwise, R' is as defined above.

[087] As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), and sulfur (S).

[088] The term "pharmaceutically acceptable salt" is meant to include a salt of the active compound which is prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compound described herein. When a compound of the invention contains relatively acidic functionalities, a base addition salt can be obtained by contacting the neutral form of such compound with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of

pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When a compound of the invention contains relatively basic functionalities, an acid addition salt can be obtained by contacting the neutral form of such compound with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginine and the like, and salts of organic acids like glucuronic or galacturonic acids and the like (see, for example, Berge et al. (1977) *J. Pharm. Sci.* 66:1-19). Certain specific compounds of the invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[089] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the invention.

[090] In addition to salt forms, the invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the invention. Additionally, prodrugs can be converted to the compounds of the invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound of the

invention which is administered as an ester (the “prodrug”), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound.

[091] As used herein, “solvate” refers to a compound of the present invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate. In some embodiments, the compounds, salts of the compounds, tautomers of the compound, and salts of the tautomers may include a solvent or water such that the compound or salt is a solvate or hydrate.

[092] Certain compounds of the invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the invention and are intended to be within the scope of the invention.

[093] As known by those skilled in the art, certain compounds of the invention may exist in one or more tautomeric forms. Because one chemical structure may only be used to represent one tautomeric form, it will be understood that convenience, referral to a compound of a given structural formula includes tautomers of the structure represented by the structural formula.

[094] Certain compounds of the invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, enantiomers, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the invention. Furthermore, atropisomers and mixtures thereof such as those resulting from restricted rotation about two aromatic or heteroaromatic rings bonded to one another are intended to be encompassed within the scope of the invention.

[095] As used herein and unless otherwise indicated, the term “stereoisomer” or “stereomerically pure” means one stereoisomer of a compound that is substantially free of other stereoisomers of that compound. For example, a stereomerically pure compound having one chiral center will be substantially free of the opposite enantiomer of the compound. A stereomerically pure compound having two chiral centers will be substantially free of other diastereomers of the compound. A typical stereomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, more preferably greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, even more preferably greater than about 95% by weight of one stereoisomer of the compound

and less than about 5% by weight of the other stereoisomers of the compound, and most preferably greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. If the stereochemistry of a structure or a portion of a structure is not indicated with, for example, bold or dashed lines, the structure or portion of the structure is to be interpreted as encompassing all stereoisomers of it. A bond drawn with a wavy line indicates that both stereoisomers are encompassed.

[096] Various compounds of the invention contain one or more chiral centers, and can exist as racemic mixtures of enantiomers, mixtures of diastereomers or enantiomerically or optically pure compounds. This invention encompasses the use of stereomerically pure forms of such compounds, as well as the use of mixtures of those forms. For example, mixtures comprising equal or unequal amounts of the enantiomers of a particular compound of the invention may be used in methods and compositions of the invention. These isomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. See, e.g., Jacques, J., et al., *Enantiomers, Racemates and Resolutions* (Wiley-Interscience, New York, 1981); Wilen, S. H., et al. (1997) *Tetrahedron* 33:2725; Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972).

[097] The compounds of the invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). Radiolabeled compounds are useful as therapeutic or prophylactic agents, research reagents, e.g., GPR40 assay reagents, and diagnostic agents, e.g., in vivo imaging agents. All isotopic variations of the compounds of the invention, whether radioactive or not, are intended to be encompassed within the scope of the invention. For example, if a variable is said to be H, this means that variable may also be deuterium (D) or tritium (T).

6.2 Embodiments of the Invention

[098] In one aspect, a class of compounds that modulates GPR40 is described herein. Depending on the biological environment (e.g., cell type, pathological condition of the subject, etc.), these compounds can modulate, e.g., activate or inhibit, the actions of GPR40. By modulating GPR40, the compounds find use as therapeutic agents capable of

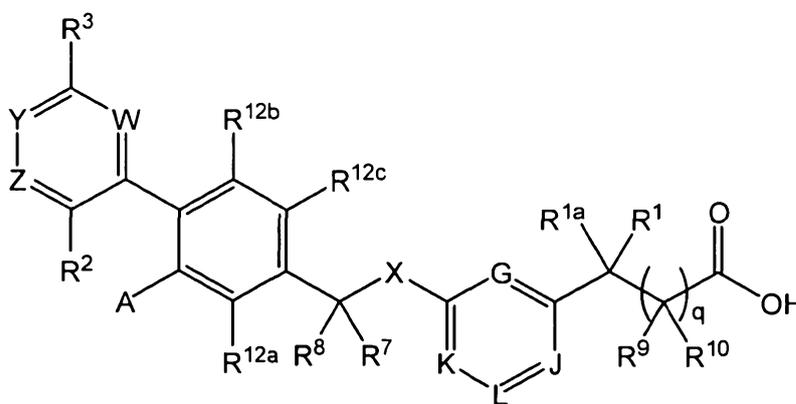
regulating insulin levels in a subject. The compounds find use as therapeutic agents for modulating diseases and conditions responsive to modulation of GPR40 and/or mediated by GPR40 and/or mediated by pancreatic β cells. As noted above, examples of such diseases and conditions include diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, cancer, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, ketoacidosis, hypoglycemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, nephropathy, thrombotic disorders, diabetic neuropathy, diabetic retinopathy, dermatopathy, dyspepsia and edema. Additionally, the compounds are useful for the treatment and/or prevention of complications of these diseases and disorders (e.g., type II diabetes, sexual dysfunction, dyspepsia and so forth).

[099] While the compounds of the invention are believed to exert their effects by interacting with GPR40, the mechanism of action by which the compounds act is not a limiting embodiment of the invention.

[0100] Compounds contemplated by the invention include, but are not limited to, the exemplary compounds provided herein.

6.2.1 Compounds

[0101] In one aspect, the present invention provides a compound having the formula **I** or a pharmaceutically acceptable salt, stereoisomer, C₁-C₆ alkyl ester, or mixture thereof:



I

where

G is selected from N or CR^{11a};

J is selected from N or CR^{11b};

L is selected from N or CR^{11c};

K is selected from N or CR^{1d};

wherein 0 or 1 of G, J, L, and K is N;

A is selected from -(C₁-C₁₂)alkyl; -(C₂-C₁₂)alkenyl; -(C₁-C₁₂)alkyl-O-(C₁-C₄)alkyl; -(C₁-C₁₂)alkyl-OH; -(C₁-C₁₂)alkyl-O-(C₂-C₄)alkenyl; -(C₂-C₁₂)alkenyl-O-(C₁-C₄)alkyl; -(C₂-C₁₂)alkenyl-OH; -(C₂-C₁₂)alkenyl-O-(C₂-C₄)alkenyl; -O-(C₁-C₁₂)alkyl; -O-(C₂-C₁₂)alkenyl; -O-(C₁-C₄)alkyl-aryl; -S-(C₁-C₁₂)alkyl; -S-(C₂-C₁₂)alkenyl; -S(O)-(C₁-C₁₂)alkyl; -S(O)-(C₂-C₁₂)alkenyl; -S(O)₂-(C₁-C₁₂)alkyl; -S(O)₂-(C₂-C₁₂)alkenyl; a heterocycle comprising 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; a -(C₁-C₄)alkyl-heterocyclyl wherein the heterocyclyl of the -(C₁-C₄)alkyl-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; or a -O-heterocyclyl wherein the heterocyclyl of the -O-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; further wherein the alkyl and alkenyl groups of -(C₁-C₁₂)alkyl, -(C₂-C₁₂)alkenyl, -(C₁-C₁₂)alkyl-O-(C₁-C₄)alkyl, -(C₁-C₁₂)alkyl-O-H, -(C₁-C₁₂)alkyl-O-(C₂-C₄)alkenyl, -(C₂-C₁₂)alkenyl-O-(C₁-C₄)alkyl, -(C₂-C₁₂)alkenyl-OH, -(C₂-C₁₂)alkenyl-O-(C₂-C₄)alkenyl, -O-(C₁-C₁₂)alkyl, -O-(C₂-C₁₂)alkenyl, and -O-(C₁-C₄)alkyl-aryl are unsubstituted or are substituted with from 1 to 4 substituents selected from -F, -Cl, -OH, (=O), -NH₂, NH(C₁-C₄)alkyl, -N((C₁-C₄)alkyl)₂, aryl, unsubstituted -(C₁-C₂)alkyl, or unsubstituted -O-(C₁-C₂)alkyl;

X is O, S, or NR^a wherein R^a is selected from -H or -(C₁-C₆) alkyl groups;

W, Y, and Z are selected from N or CR¹³; wherein 0, 1, or 2 of W, Y, and Z is N; and further wherein Z is not N if R² is -F;

R¹ is selected from -H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₁-C₄)alkyl-O-(C₁-C₄)alkyl, heterocyclyl, aryl, or heteroaryl;

R^{1a} is selected from -H and -(C₁-C₄)alkyl;

or R¹ and R^{1a} may join together to form a 3 to 7 membered ring with 0, 1, or 2 heteroatoms selected from O, N, or S ;

R² is selected from -H, -F, -CF₃, or -O-(C₁-C₆)alkyl;

R³ is -H, -F, -Cl, -OH, -(C₁-C₄)alkyl, -O-(C₁-C₃)alkyl, or -S-(C₁-C₂)alkyl;

R^7 and R^8 are independently selected from -H and -(C₁-C₄)alkyl;
 R^9 and R^{10} are independently selected from -H and -(C₁-C₄)alkyl;
 each of R^{11a} , R^{11b} , R^{11c} , and R^{11d} is independently selected from -H, -F, -Cl, -(C₁-C₄)alkyl, or -O-(C₁-C₄)alkyl; and R^{11a} is absent if G is N; R^{11b} is absent if J is N, R^{11c} is absent if L is N; or R^{11d} is absent if K is N;
 each of R^{12a} , R^{12b} , and R^{12c} is independently selected from -H, -F, -Cl, -(C₁-C₄)alkyl, or -O-(C₁-C₄)alkyl;
 R^{13} is selected from -H, -F, -(C₁-C₄)alkyl, and -O-(C₁-C₄)alkyl; and
 q is 1 or 2.

[0102] In another aspect, the invention provides a compound of formula I or a pharmaceutically acceptable salt, stereoisomer, C₁-C₆ alkyl ester, or mixture thereof, wherein

G is selected from N or CR^{11a};
 J is selected from N or CR^{11b};
 L is selected from N or CR^{11c};
 K is selected from N or CR^{11d};
 wherein 0 or 1 of G, J, L, and K is N;
 A is selected from (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, -O-(C₁-C₁₂)alkyl, -O-(C₂-C₁₂)alkenyl, -O-(C₁-C₄)alkyl-aryl, or a heterocycle comprising 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N or O, wherein the heterocycle has 0 or 1 double bond between ring members;
 X is O, S, or NR^a wherein R^a is selected from H or (C₁-C₆) alkyl groups;
 W , Y , and Z are selected from N or CR¹³; wherein 0 or 1 of W, Y, and Z is N;
 and further wherein Z is not N if R² is F;
 R^1 is selected from H, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -(C₁-C₄)alkyl-O-(C₁-C₄)alkyl, heterocyclyl, aryl, or heteroaryl;
 R^{1a} is selected from H and (C₁-C₄)alkyl;
 R^2 is selected from H, F, CF₃, or (C₁-C₆)alkoxy;
 R^3 is H, -OH, -O(C₁-C₂)alkyl, or -S(C₁-C₂)alkyl;
 R^7 and R^8 are independently selected from H and (C₁-C₄)alkyl;
 R^9 and R^{10} are independently selected from H and (C₁-C₄)alkyl;
 each of R^{11a} , R^{11b} , R^{11c} , and R^{11d} is independently selected from H, F, Cl, (C₁-C₄)alkyl, or (C₁-C₄)alkoxy; and R^{11a} is absent if G is N; R^{11b} is absent if J is N, R^{11c} is absent if L is N; or R^{11d} is absent if K is N;

each of R^{12a} , R^{12b} , and R^{12c} is independently selected from H, F, Cl, (C₁-C₄)alkyl, or (C₁-C₄)alkoxy;

R^{13} is selected from H, F, (C₁-C₄)alkyl, and -O-(C₁-C₄)alkyl; and
q is 1 or 2.

[0103] In another aspect, the invention provides a compound of formula I or a pharmaceutically acceptable salt, stereoisomer, C₁-C₆ alkyl ester, or mixture thereof, wherein

G is selected from N or CR^{11a};

J is selected from N or CR^{11b};

L is selected from N or CR^{11c};

K is selected from N or CR^{11d};

wherein 0 or 1 of G, J, L, and K is N;

A is selected from (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, -O-(C₁-C₁₂)alkyl, -O-(C₂-C₁₂)alkenyl, -O-(C₁-C₄)alkyl-aryl, or a heterocycle comprising 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N or O, wherein the heterocycle has 0 or 1 double bond between ring members;

X is O or S;

W, Y, and Z are selected from N or CR¹³; wherein 0 or 1 of W, Y, and Z is N; and further wherein Z is not N if R² is F;

R¹ is selected from H, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -(C₁-C₄)alkyl-O-(C₁-C₄)alkyl, heterocyclyl, aryl, or heteroaryl;

R^{1a} is selected from H and (C₁-C₄)alkyl;

R² is selected from H, F, CF₃, or (C₁-C₆)alkoxy;

R³ is H, -OH, -O-(C₁-C₂)alkyl, or -S-(C₁-C₂)alkyl;

R⁷ and R⁸ are independently selected from H and (C₁-C₄)alkyl;

R⁹ and R¹⁰ are independently selected from H and (C₁-C₄)alkyl;

each of R^{11a}, R^{11b}, R^{11c}, and R^{11d} is independently selected from H, F, Cl, (C₁-C₄)alkyl, or (C₁-C₄)alkoxy; and R^{11a} is absent if G is N; R^{11b} is absent if J is N, R^{11c} is absent if L is N; or R^{11d} is absent if K is N;

each of R^{12a} , R^{12b} , and R^{12c} is independently selected from H, F, Cl, (C₁-C₄)alkyl, or (C₁-C₄)alkoxy;

R^{13} is selected from H, F, (C₁-C₄)alkyl, and -O-(C₁-C₄)alkyl; and

q is 1 or 2.

[0104] In some embodiments,

X is O, S, or NR^a wherein R^a is selected from H or unsubstituted (C₁-C₆) alkyl groups;

R¹ is selected from H, unsubstituted -(C₁-C₆)alkyl, unsubstituted -(C₂-C₆)alkenyl, unsubstituted -(C₂-C₆)alkynyl, -(C₁-C₄)alkyl-O-(C₁-C₄)alkyl, heterocyclyl, aryl, heteroaryl, -(C₁-C₆)alkyl substituted with from 1 to 3 substituents selected from -F or -OH, or -(C₂-C₆)alkenyl substituted with from 1 to 3 substituents selected from -F or -OH;

R^{1a} is selected from H, unsubstituted -(C₁-C₄)alkyl, or -(C₁-C₄)alkyl substituted with from 1 to 3 substituents selected from F and OH;

or R¹ and R^{1a} may join together to form a 3 to 7 membered ring with 0, 1, or 2 heteroatoms selected from O, N, or S;

R² is selected from -H, -F, -CF₃, or -O-(C₁-C₆)alkyl;

R³ is -H, -F, -Cl, -OH, -S(C₁-C₂)alkyl, unsubstituted -(C₁-C₄)alkyl, unsubstituted -O(C₁-C₃)alkyl, -(C₁-C₄) alkyl substituted with from 1 to 3 substituents selected from -F, -OH, (=O), or -O(C₁-C₂)alkyl, or substituted -O(C₁-C₃)alkyl, wherein the alkyl group of the substituted -O(C₁-C₃)alkyl is substituted with from 1 to 3 substituents selected from -F, -OH, or -O(C₁-C₂)alkyl;

R⁷ and R⁸ are independently selected from H and unsubstituted -(C₁-C₄)alkyl;

R⁹ and R¹⁰ are independently selected from H and unsubstituted -(C₁-C₄)alkyl;

each of R^{11a}, R^{11b}, R^{11c}, and R^{11d} is independently selected from -H, -F, -Cl, -(C₁-C₄)alkyl, -O(C₁-C₄)alkyl, or -CF₃; and R^{11a} is absent if G is N; R^{11b} is absent if J is N, R^{11c} is absent if L is N; or R^{11d} is absent if K is N;

each of R^{12a}, R^{12b}, and R^{12c} is independently selected from -H, -F, -Cl, unsubstituted -(C₁-C₄)alkyl, CF₃, or -O(C₁-C₄)alkyl; and

R¹³ is selected from -H, -F, -(C₁-C₄)alkyl, and -O-(C₁-C₄)alkyl. In some such embodiments, q is 1.

[0105] In some embodiments, R¹ is selected from H, unsubstituted -(C₁-C₆)alkyl, unsubstituted -(C₂-C₆)alkenyl, unsubstituted -(C₂-C₆)alkynyl, -(C₁-C₄)alkyl-O-(C₁-C₄)alkyl, heterocyclyl, aryl, heteroaryl, -(C₁-C₆)alkyl substituted with from 1 to 3 substituents selected from -F or -OH, or -(C₂-C₆)alkenyl substituted with from 1 to 3 substituents selected from -F or -OH.

[0106] In some embodiments, R^{1a} is selected from H, unsubstituted -(C₁-C₄)alkyl, or -(C₁-C₄)alkyl substituted with from 1 to 3 substituents selected from F and

OH; or R¹ and R^{1a} may join together to form a 3 to 7 membered ring with 0, 1, or 2 heteroatoms selected from O, N, or S.

[0107] In some embodiments, R³ is -H, -F, -Cl, -OH, -S(C₁-C₂)alkyl, unsubstituted -(C₁-C₄)alkyl, unsubstituted -O(C₁-C₃)alkyl, -(C₁-C₄) alkyl substituted with from 1 to 3 substituents selected from -F, -OH, (=O), or -O(C₁-C₂)alkyl, or substituted -O(C₁-C₃)alkyl, wherein the alkyl group of the substituted -O(C₁-C₃)alkyl is substituted with from 1 to 3 substituents selected from -F, -OH, or -O(C₁-C₂)alkyl.

[0108] In some embodiments, R⁷ and R⁸ are independently selected from H and unsubstituted -(C₁-C₄)alkyl.

[0109] In some embodiments, R⁹ and R¹⁰ are independently selected from H and unsubstituted -(C₁-C₄)alkyl.

[0110] In some embodiments, each of R^{11a}, R^{11b}, R^{11c}, and R^{11d} is independently selected from -H, -F, -Cl, -(C₁-C₄)alkyl, -O(C₁-C₄)alkyl, or -CF₃; and R^{11a} is absent if G is N; R^{11b} is absent if J is N, R^{11c} is absent if L is N; or R^{11d} is absent if K is N.

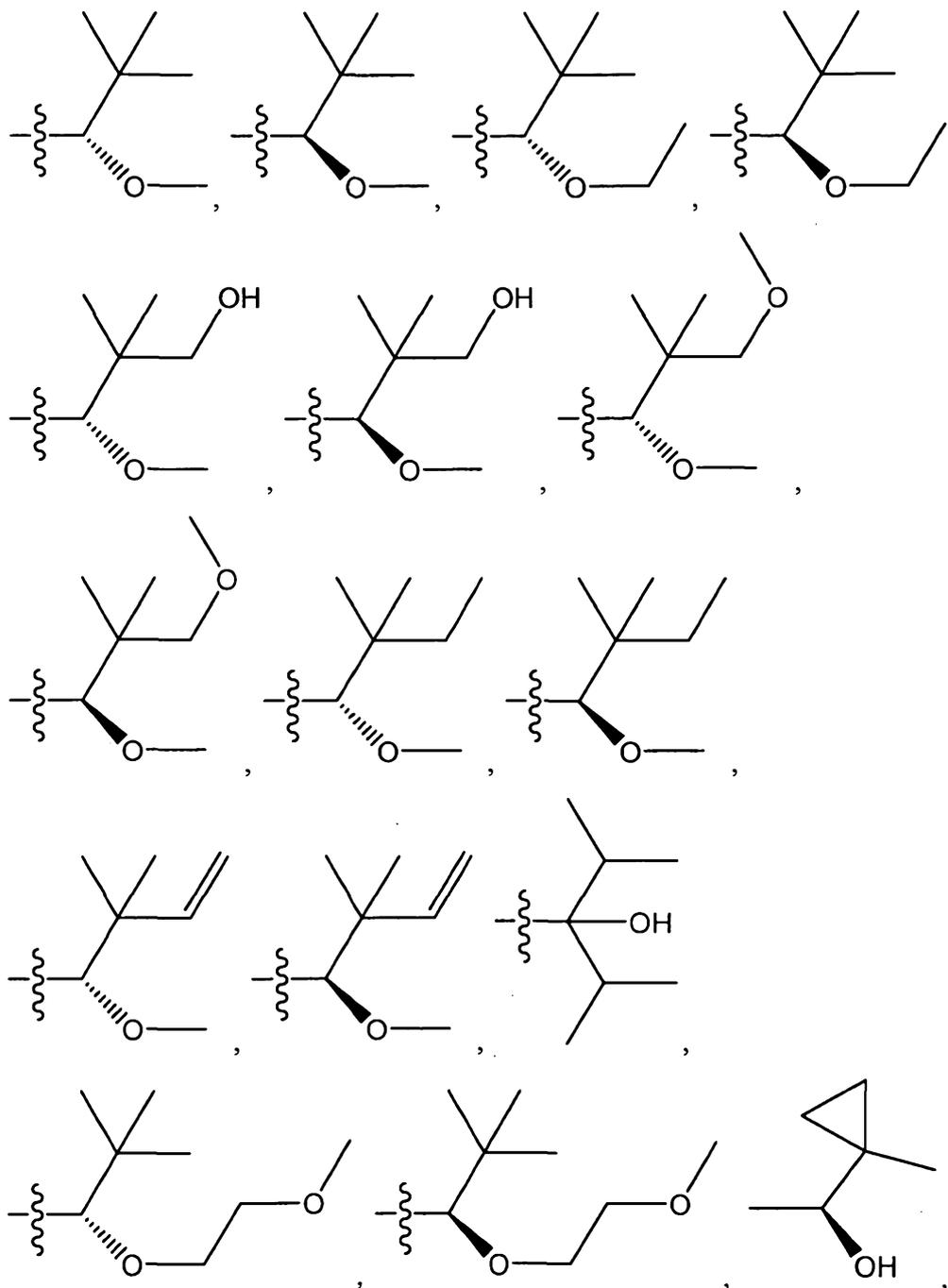
[0111] In some embodiments, each of R^{12a}, R^{12b}, and R^{12c} is independently selected from -H, -F, -Cl, unsubstituted -(C₁-C₄)alkyl, CF₃, or -O(C₁-C₄)alkyl.

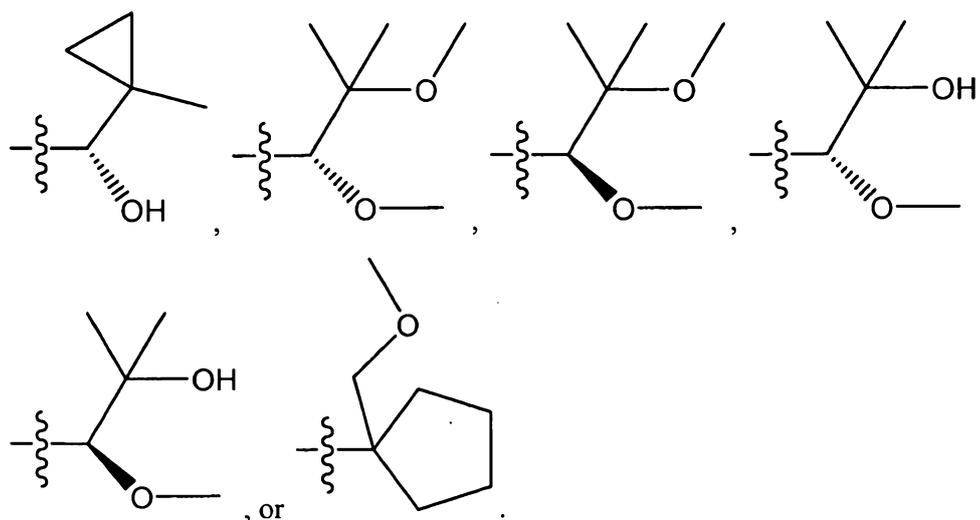
[0112] In some embodiments, R¹³ is selected from -H, -F, -(C₁-C₄)alkyl, and -O-(C₁-C₄)alkyl.

[0113] In some embodiments, A is selected from -(C₄-C₁₂)alkyl, -(C₄-C₁₂)alkenyl, -(C₃-C₁₂)alkyl-O-(C₁-C₄)alkyl, -(C₃-C₁₂)alkyl-OH, -(C₃-C₁₂)alkenyl-O-(C₁-C₄)alkyl, -(C₃-C₁₂)alkenyl-OH, -O-(C₄-C₁₂)alkyl, -O-(C₄-C₁₂)alkenyl, a heterocycle comprising 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N or O, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups, a -(C₁-C₄)alkyl-heterocyclyl wherein the heterocyclyl of the -(C₁-C₄)alkyl-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N or O, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups, or a -O-heterocyclyl wherein the heterocyclyl of the -O-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N or O, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups, further wherein the alkyl and alkenyl groups of -(C₄-C₁₂)alkyl, -(C₄-C₁₂)alkenyl, -(C₃-C₁₂)alkyl-O-(C₁-C₄)alkyl, -(C₃-C₁₂)alkyl-OH, -(C₃-C₁₂)alkenyl-O-(C₁-

C_4 alkyl, $-(C_3-C_{12})$ alkenyl-OH, $-O-(C_4-C_{12})$ alkyl, or $-O-(C_4-C_{12})$ alkenyl are unsubstituted or are substituted with from 1 to 4 substituents selected from -F, -Cl, -OH, (=O), $-NH_2$, $NH(C_1-C_4)$ alkyl, $-N((C_1-C_4)alkyl)_2$, aryl, unsubstituted $-O-(C_1-C_2)$ alkyl, or unsubstituted $-(C_1-C_2)$ alkyl. In some such embodiments, A is selected from $-(C_4-C_{12})$ alkyl, $-(C_4-C_{12})$ alkenyl, $-(C_3-C_{12})$ alkyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkyl-OH, $-(C_3-C_{12})$ alkenyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkenyl-OH, $-O-(C_4-C_{12})$ alkyl, or $-O-(C_4-C_{12})$ alkenyl, wherein the alkyl and alkenyl groups of $-(C_4-C_{12})$ alkyl, $-(C_4-C_{12})$ alkenyl, $-(C_3-C_{12})$ alkyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkyl-O-H, $-(C_3-C_{12})$ alkenyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkenyl-OH, $-O-(C_4-C_{12})$ alkyl, or $-O-(C_4-C_{12})$ alkenyl are unsubstituted or are substituted with from 1 to 4 substituents selected from -F, -Cl, -OH, (=O), $-NH_2$, $NH(C_1-C_4)$ alkyl, or $N((C_1-C_4)alkyl)_2$, unsubstituted $-O-(C_1-C_2)$ alkyl, or unsubstituted $-(C_1-C_2)$ alkyl. In some such embodiments, A is selected from $-(C_4-C_{12})$ alkyl, $-(C_4-C_{12})$ alkenyl, $-(C_3-C_{12})$ alkyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkyl-OH, $-(C_3-C_{12})$ alkenyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkenyl-OH, wherein the alkyl and alkenyl groups of $-(C_4-C_{12})$ alkyl, $-(C_4-C_{12})$ alkenyl, $-(C_3-C_{12})$ alkyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkyl-O-H, $-(C_3-C_{12})$ alkenyl-O- (C_1-C_4) alkyl, or $-(C_3-C_{12})$ alkenyl-OH, are unsubstituted or are substituted with from 1 to 4 substituents selected from -F, -OH, unsubstituted $-O-(C_1-C_2)$ alkyl, or unsubstituted $-(C_1-C_2)$ alkyl. In some such embodiments, A is selected from $-(C_4-C_{12})$ alkyl, $-(C_4-C_{12})$ alkenyl, $-(C_3-C_{12})$ alkyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkyl-OH, $-(C_3-C_{12})$ alkenyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkenyl-OH, wherein the alkyl and alkenyl groups of $-(C_4-C_{12})$ alkyl, $-(C_4-C_{12})$ alkenyl, $-(C_3-C_{12})$ alkyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkyl-O-H, $-(C_3-C_{12})$ alkenyl-O- (C_1-C_4) alkyl, or $-(C_3-C_{12})$ alkenyl-OH, are unsubstituted or are substituted with 1 to 4 substituent selected from -F, -OH, unsubstituted $-O-(C_1-C_2)$ alkyl, or unsubstituted $-(C_1-C_2)$ alkyl. In some such embodiments, A is a 5 to 7 membered cycloalkyl or cycloalkenyl group comprising from 1 to 4 methyl groups. In other embodiments, A is a $-(C_3-C_{12})$ alkyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkyl-OH, $-(C_3-C_{12})$ alkenyl-O- (C_1-C_4) alkyl, or $-(C_3-C_{12})$ alkenyl-OH. In some embodiments, each of the alkyl and alkenyl groups of the $-(C_3-C_{12})$ alkyl-O- (C_1-C_4) alkyl, $-(C_3-C_{12})$ alkyl-OH, $-(C_3-C_{12})$ alkenyl-O- (C_1-C_4) alkyl, or $-(C_3-C_{12})$ alkenyl-OH are unsubstituted whereas in other embodiments, each is substituted with 1 to 4 substituents selected from -OH, unsubstituted $-O-(C_1-C_2)$ alkyl, or unsubstituted $-(C_1-C_2)$ alkyl. In some embodiments, A is a $-(C_4-C_8)$ alkyl-O- (C_1-C_2) alkyl, $-(C_4-C_8)$ alkyl-OH, $-(C_4-C_8)$ alkenyl-O- (C_1-C_2) alkyl, or $-(C_4-C_8)$ alkenyl-OH and each of the alkyl and alkenyl groups of $-(C_4-C_8)$ alkyl-O- (C_1-C_2) alkyl, $-(C_4-C_8)$ alkyl-OH, $-(C_4-C_8)$ alkenyl-O- (C_1-C_2) alkyl, or $-(C_4-C_8)$ alkenyl-OH are unsubstituted or are substituted with 1 substituent

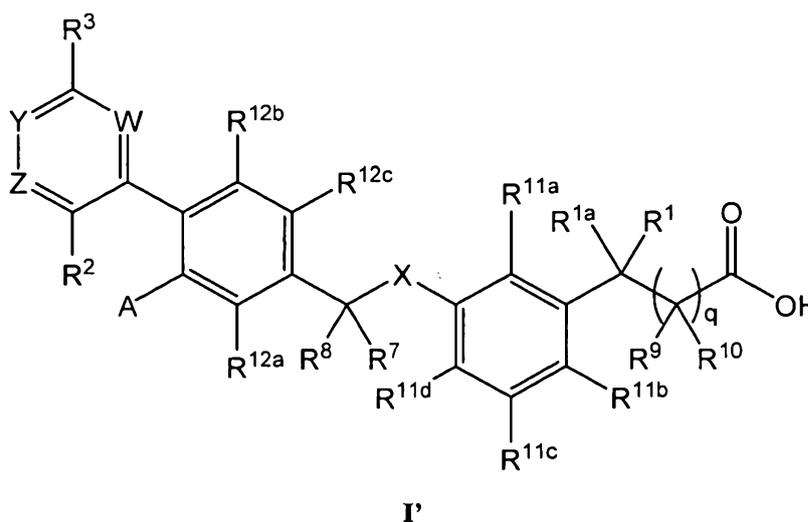
selected from $-OH$, unsubstituted $-O-(C_1-C_2)alkyl$, or unsubstituted $-(C_1-C_2)alkyl$. In some such embodiments, at least one of the alkyl or alkenyl groups is branched or comprises a C_3-C_7 cycloalkyl ring. Therefore, in some embodiments, A is selected from





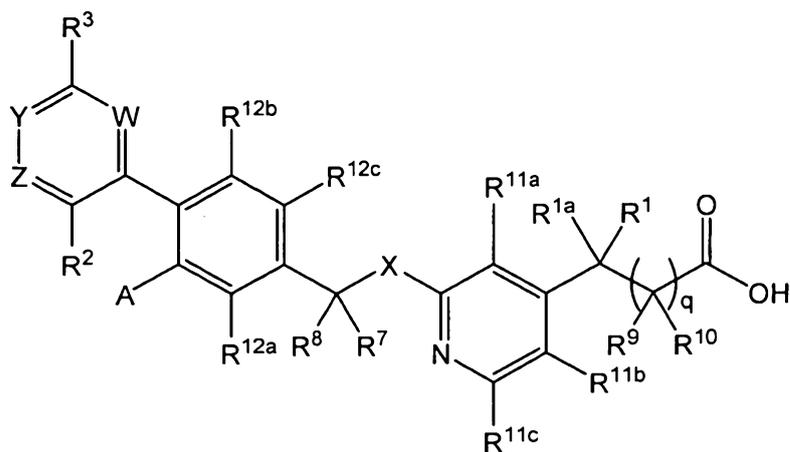
[0114] In some embodiments, X is O. In other embodiments, X is S. In still further embodiments X is NR^a . In some embodiments X is NR^a and R^a is selected from H or methyl. In still other embodiments, X is NR^a and R^a is H.

[0115] In some embodiments, the compound of formula I is a compound of formula I' or a pharmaceutically acceptable salt, stereoisomer, C_1 - C_6 alkyl ester, or mixture thereof,



where the variables have the values described above with respect to the compound of formula I.

[0116] In some embodiments, the compound of formula I is a compound of formula I' or a pharmaceutically acceptable salt, stereoisomer, C_1 - C_6 alkyl ester, or mixture thereof:



I'

where the variables have the values described above with respect to the compound of formula I.

[0117] In some embodiments, G is CR^{11a}; J is CR^{11b}; L is CR^{11c}; and K is CR^{11d}. In some such embodiments, each of R^{11a}, R^{11b}, R^{11c}, and R^{11d} is H. In some such embodiments, each of R^{12a}, R^{12b}, and R^{12c} is H. In other such embodiments, R^{12a} and R^{12b} are H and R^{12c} is F. In still other such embodiments, R^{12b} and R^{12c} are H and R^{12a} is F. In yet other such embodiments, R^{12a} and R^{12c} are H and R^{12b} is F. In other such embodiments, R^{11a} is F and each of R^{11b}, R^{11c}, and R^{11d} is H. In other such embodiments, R^{11b} is F and each of R^{11a}, R^{11c}, and R^{11d} is H. In other such embodiments, R^{11c} is F and each of R^{11a}, R^{11b}, and R^{11d} is H. In other such embodiments, R^{11d} is F and each of R^{11a}, R^{11b}, and R^{11c} is H. In other embodiments, where R^{11a}, R^{11b}, R^{11c}, and R^{11d} is H or where R^{11a} is F and each of R^{11b}, R^{11c}, and R^{11d} is H, R^{12c} is F, R^{12a} is H, and R^{12b} is H.

[0118] In some embodiments, G is CR^{11a}; J is CR^{11b}; L is CR^{11c}; and K is N. In some such embodiments, each of R^{11a}, R^{11b}, and R^{11c} is H. In some such embodiments, each of R^{12a}, R^{12b}, and R^{12c} is H. In some such embodiments R^{1a} is H; W is C-H; Y, is C-H; Z is C-H; R⁷ is H; R⁸ is H; R⁹ is H; R¹⁰ is H; X is O, and q is 1. In still other such embodiments, R² is F. In some such embodiments, R³ is methoxy or ethoxy.

[0119] In some embodiments, G is N; J is CR^{11b}; L is CR^{11c}; and K is CR^{11d}. In some such embodiments, each of R^{11b}, R^{11c}, and R^{11d} is H. In some such embodiments, each of R^{12a}, R^{12b}, and R^{12c} is H.

[0120] In some embodiments, G is CR^{11a}; J is N; L is CR^{11c}; and K is CR^{11d}. In some such embodiments, each of R^{11a}, R^{11c}, and R^{11d} is H. In some such embodiments, each of R^{12a}, R^{12b}, and R^{12c} is H.

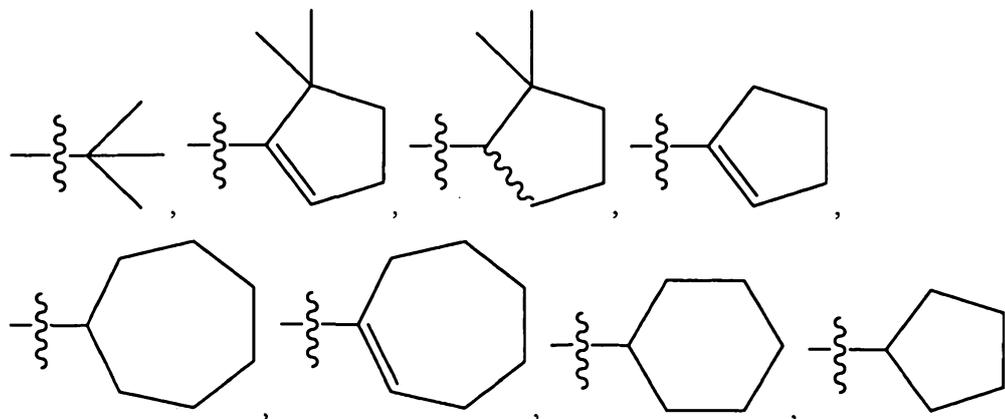
[0121] In some embodiments, G is CR^{11a}; J is CR^{11b}; L is N; and K is CR^{11d}. In some such embodiments, each of R^{11a}, R^{11b}, and R^{11d} is H. In some such embodiments, each of R^{12a}, R^{12b}, and R^{12c} is H.

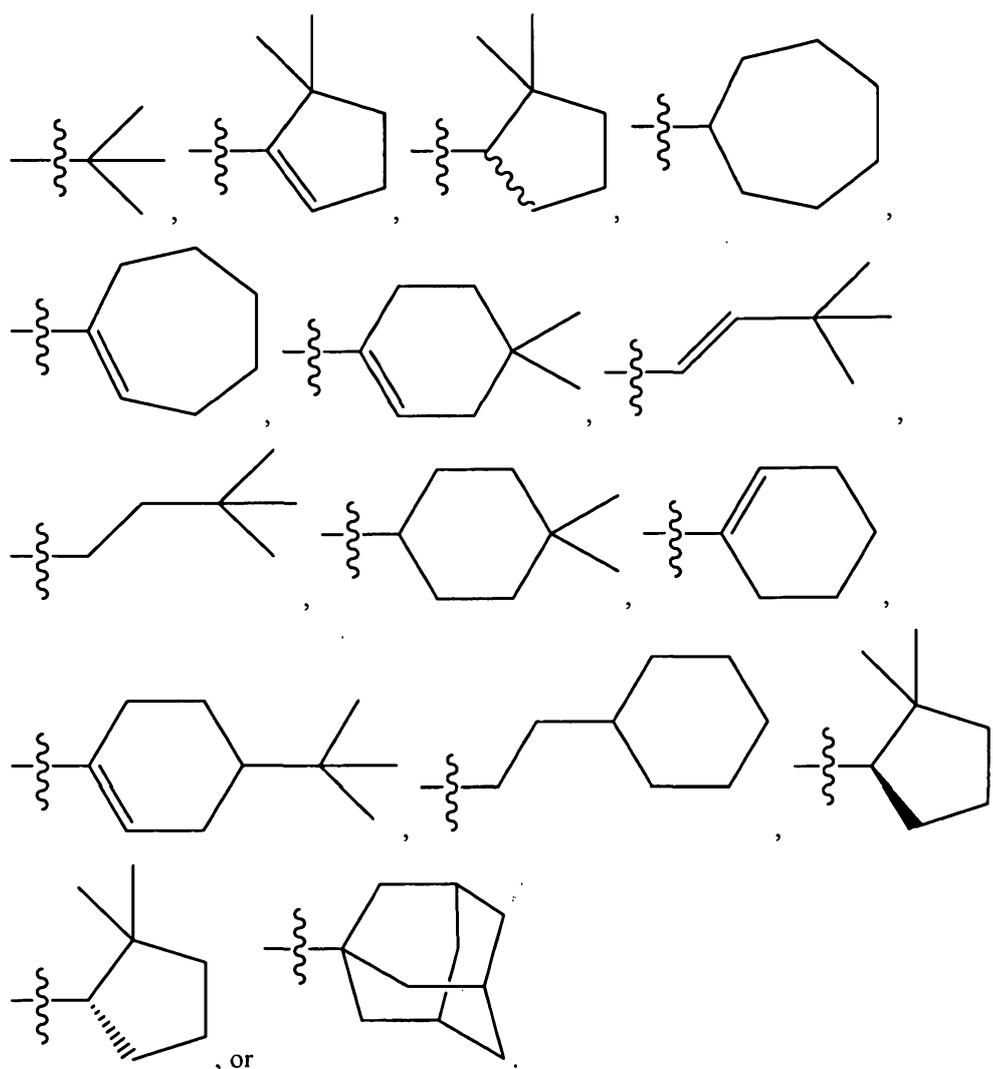
[0122] In some embodiments, G is CR^{11a}; J is CR^{11b}; L is CR^{11c}; K is CR^{11d}; R^{11a}, R^{11b}, R^{11c}, and R^{11d} are H; R^{1a} is H; W is C-H; Z is C-H; R² is F; R³ is methoxy; R⁷ is H; R⁸ is H; R⁹ is H; R¹⁰ is H; X is O; q is 1; and two of R^{12a}, R^{12b}, and R^{12c} are H and the other of R^{12a}, R^{12b}, and R^{12c} is F. In some such embodiments, Y is N.

[0123] In some embodiments of the compound of formula I or I', R² is selected from F, CF₃, or (C₁-C₆)alkoxy. In some such embodiments, R² is selected from F, CF₃, or (C₄-C₆)alkoxy. In some embodiments, R² is H or F. In other embodiments, R² is F. In still other embodiments, R² is H. In other embodiments, R² is propoxy, butoxy, or pentoxy. In some such embodiments, R² is butoxy.

[0124] In some embodiments, A is selected from (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, -O-(C₁-C₁₂)alkyl, -O-(C₂-C₁₂)alkenyl, or -O-(C₁-C₄)alkyl-aryl.

[0125] In some embodiments, R² is H or F, and A is selected from a branched (C₄-C₁₀)alkyl group, a (C₄-C₁₀)alkenyl group, a bicyclic (C₇-C₁₂)alkyl group, an unsubstituted or a substituted (C₅-C₇)cycloalkyl group, or an unsubstituted or a substituted (C₅-C₇)cycloalkenyl group. In some embodiments, A is a an unsubstituted (C₅-C₇)cycloalkyl group, a (C₅-C₇)cycloalkyl group substituted with 1, 2, 3, or 4 methyl groups, an unsubstituted (C₅-C₇)cycloalkenyl group, or a (C₅-C₇)cycloalkenyl group substituted with 1, 2, 3, or 4 methyl groups. In some such embodiments, R¹ is selected from methyl, ethyl, propyl, cyclopropyl, cyclobutyl, or cyclopropylmethyl. In some such embodiments, R³ is methoxy. In some such embodiments, A is selected from





[0126] In some embodiments of the compound of formula I or I', R³ is selected from -OH, -O(C₁-C₂)alkyl, or -S(C₁-C₂)alkyl. In some such embodiments, R³ is selected from -O(C₁-C₂)alkyl or -S(C₁-C₂)alkyl. In some embodiments, R³ is selected from -O-Me or -S-Me. In other such embodiments R³ is -O-Et. In still other such embodiments, R³ is selected from -O-(C₁-C₂)haloalkyl. Examples of some such groups include -OCF₃ and -OCH₂CF₃. In some embodiments, R³ is selected from methoxy or ethoxy. In other embodiments, R³ is a substituted (C₁-C₂)alkyl group such as a -CHF₂ or -CF₃ group. In other embodiments, R³ is a (C₁-C₃)alkyl group that is substituted with a group such as -OH or with an oxo group. Examples of such groups include, but are not limited to, -C(CH₃)₂OH and -C(=O)-CH₃. In some embodiments, R³ is selected from -F, -Cl, -OH, -OCH₃, -SCH₃, -OCH₂CH₃, -OCHF₂, -OCF₃, -OCH₂CF₃, -O-cyclopropyl, -CHF₂, -CF₃,

-C(=O)-CH₃, -CH(CH₃)₂OH, or -CH₂CH₃. In some such embodiments, R³ is selected from -OCH₃, -OCH₂CH₃, -OCHF₂, -OCF₃, -OCH₂CF₃, -O-cyclopropyl, -CHF₂, or -CF₃. In some embodiments, R³ is selected from -F, -Cl, -OCHF₂, -OCH₂CF₃, -OCF₃, -O-cyclopropyl, -CF₃, or -CHF₂. In some embodiments, R³ is selected from -OCHF₂, -OCH₂CF₃, -OCF₃, -O-cyclopropyl, -CF₃, or -CHF₂.

[0127] In some embodiments of the compound of formula I or I', q is 1.

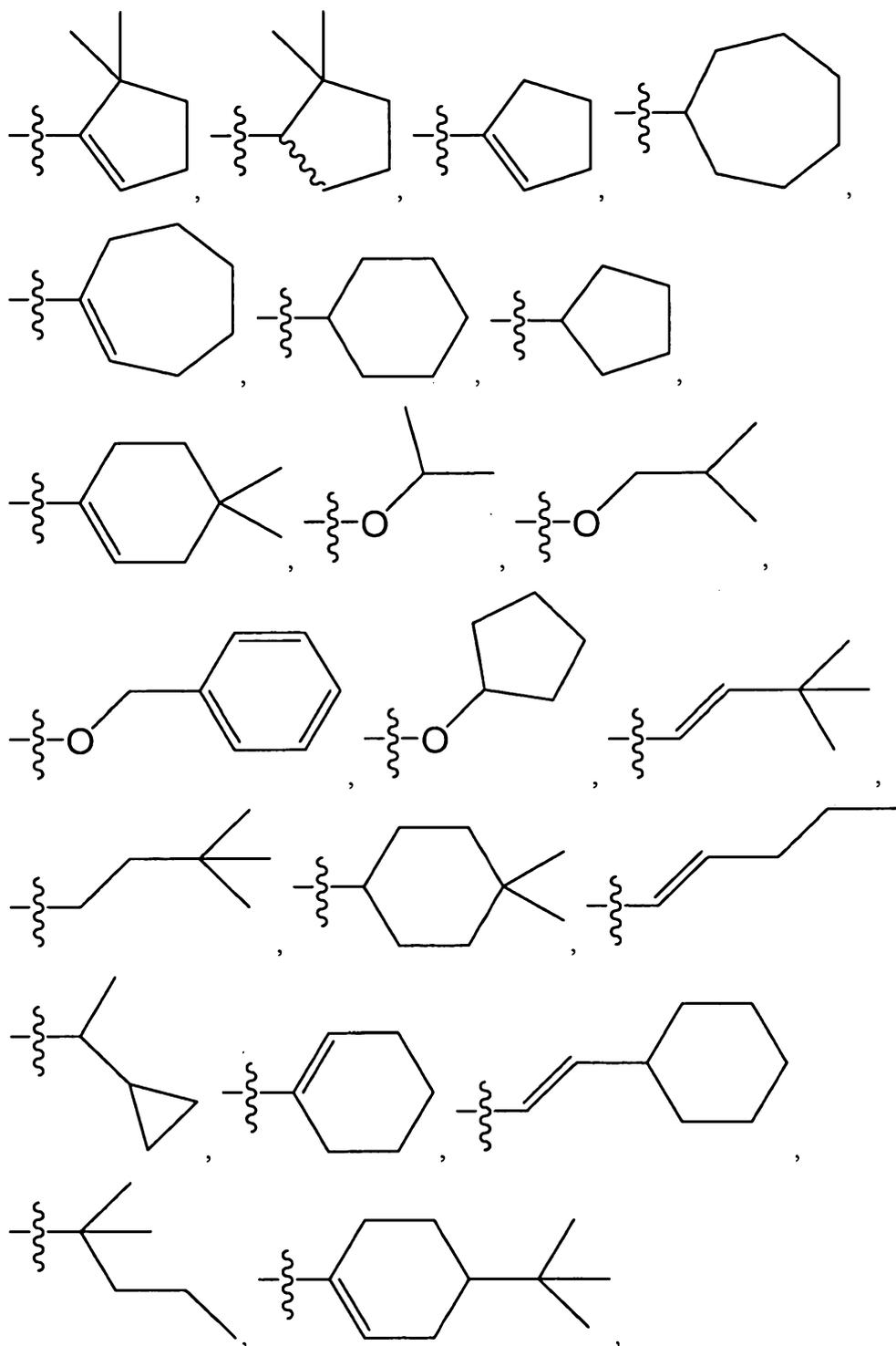
[0128] In some embodiments of the compound of formula I or I', R^{1a} is H or methyl. In some such embodiments, R^{1a} is H.

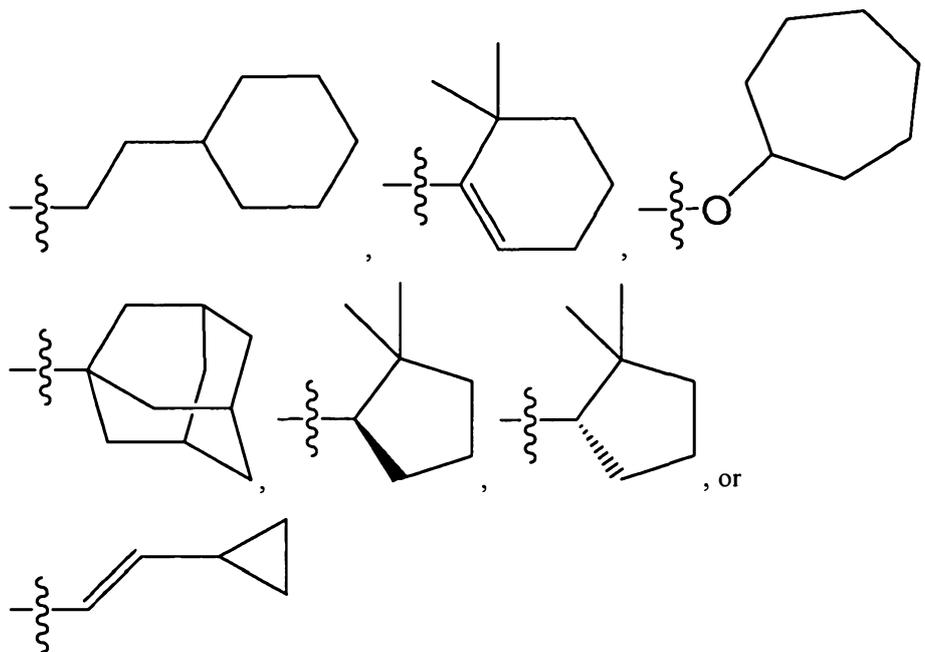
[0129] In some embodiments of the compound of formula I or I', R¹ and R^{1a} join together to form a ring having 3 to 7 ring members. In some such embodiments, R¹ and R^{1a} join to form a cycloalkyl ring such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl ring. In other embodiments, the ring has 3 to 7 ring members and includes 1 heteroatom selected from O, S, or N.

[0130] In some embodiments of the compound of formula I or I', W, Y, and Z are all C-H. In other embodiments W and Z are C-H and Y is N.

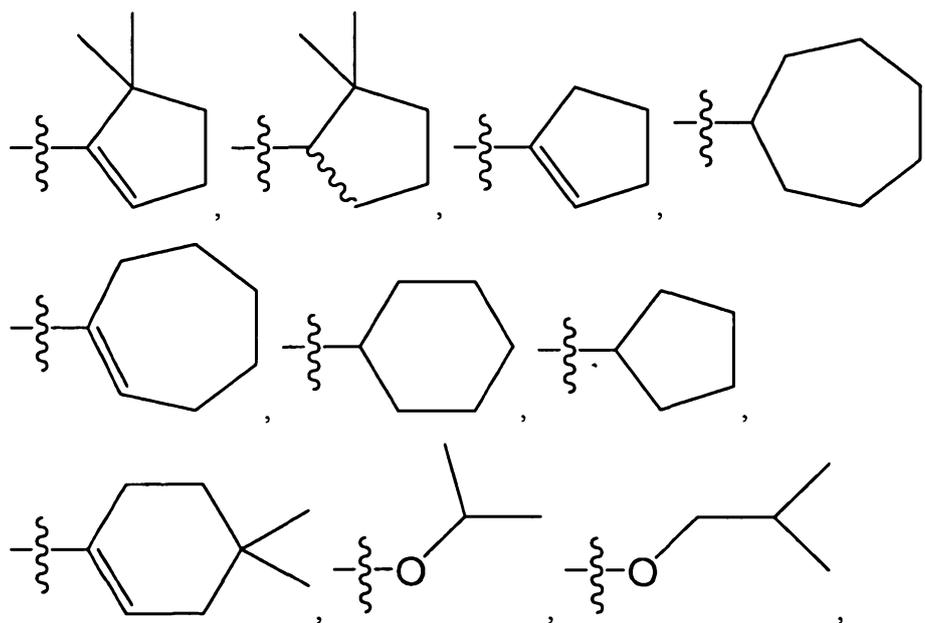
[0131] In some embodiments of the compound of formula I or I', A is selected from (C₃-C₁₀)alkyl or (C₄-C₁₀)alkenyl. In some such embodiments, A is t-butyl. In other such embodiments, A is an unsubstituted or substituted cyclopentyl, cyclohexyl, or cycloheptyl group. In some such embodiments, A is an unsubstituted cyclopentyl, cyclohexyl, or cycloheptyl group. In some such embodiments, A is a cyclopentyl, cyclohexyl, or cycloheptyl group optionally substituted with 1, 2, 3, or 4 (C₁-C₄)alkyl groups. In some such embodiments, A is a cyclopentyl, cyclohexyl, or cycloheptyl group substituted with a t-butyl group. In other such embodiments A is a cyclopentyl, cyclohexyl, or cycloheptyl group substituted with 1 or 2 methyl groups. In some such embodiments, A is an unsubstituted or substituted cyclopentenyl, cyclohexenyl, or cycloheptenyl group. In some such embodiments, A is an unsubstituted cyclopentenyl, cyclohexenyl, or cycloheptenyl group. In some such embodiments, A is a cyclopentenyl, cyclohexenyl, or cycloheptenyl group optionally substituted with 1, 2, 3, or 4 (C₁-C₄)alkyl groups. In some such embodiments, A is a cyclopentenyl, cyclohexenyl, or cycloheptenyl group substituted with a t-butyl group. In other such embodiments A is a cyclopentenyl, cyclohexenyl, or cycloheptenyl group substituted with 1 or 2 methyl groups.

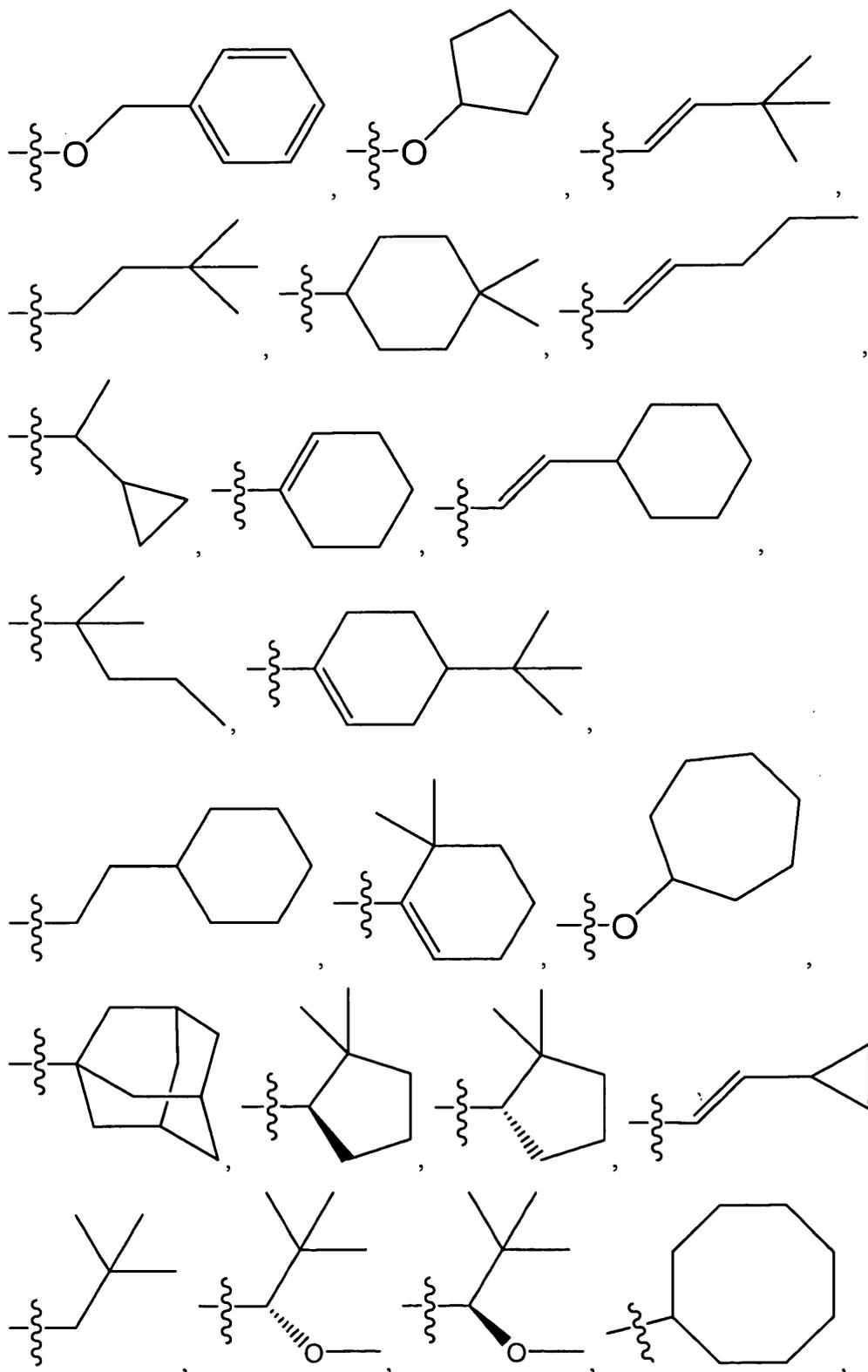
[0132] In some embodiments of the compound of formula I or I', A is selected from

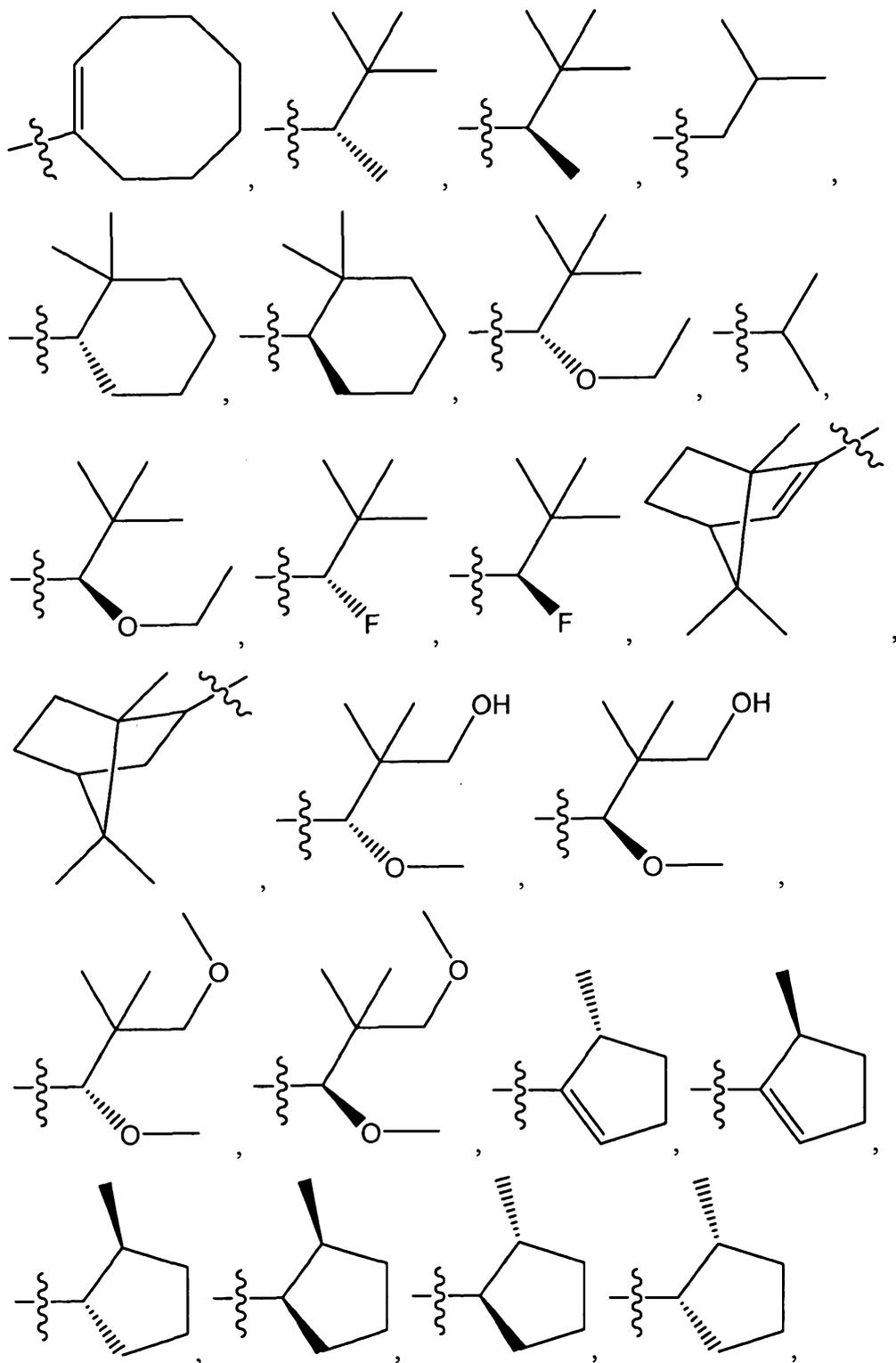


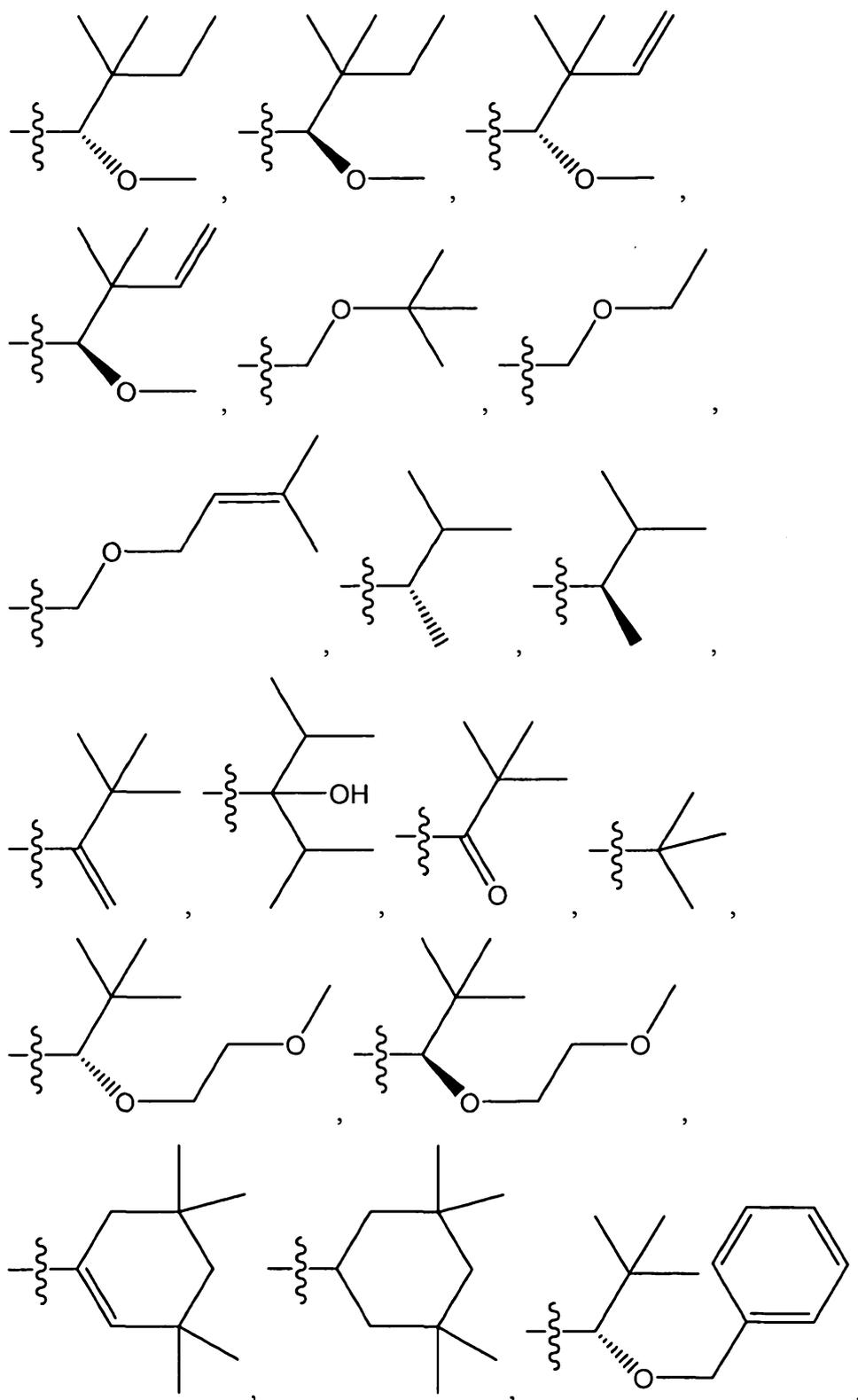


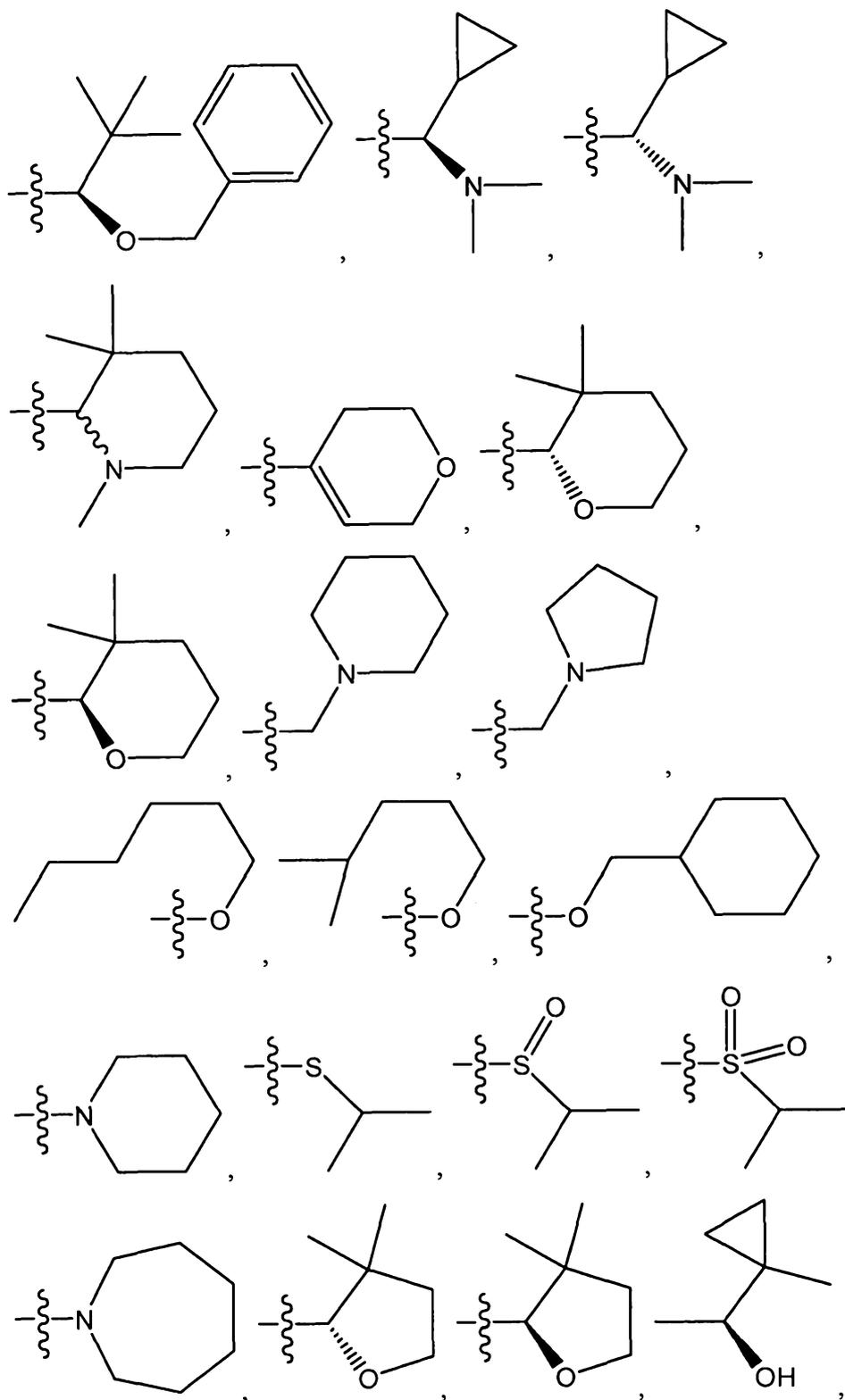
[0133] In some embodiments of the compound of formula I or I', A is selected from any one or more of









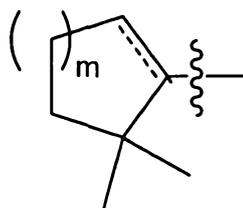


substituted saturated or partially unsaturated 3-8 membered monocyclic or bicyclic ring. In some such embodiments, R^4 , R^5 , and R^6 are independently selected from H and (C₁-C₄)alkyl groups and at least two of R^4 , R^5 , and R^6 are (C₁-C₄)alkyl groups. In some such embodiments, all three of R^4 , R^5 , and R^6 are independently selected from (C₁-C₄)alkyl groups. In some such embodiments, two of R^4 , R^5 , and R^6 are methyl groups. In some such embodiments, each of R^4 , R^5 , and R^6 is a methyl group. In other embodiments, R^4 , R^5 , and R^6 are independently selected from H, (C₁-C₄)alkyl groups, or a substituted (C₁-C₄)alkyl group selected from (C₁-C₄)haloalkyl groups, (C₁-C₄)perhaloalkyl groups, or (C₁-C₄)alkoxy(C₁-C₄)alkyl groups. In some such embodiments, at least one of R^4 , R^5 , and R^6 is a CF₃ group. In other embodiments at least one of R^4 , R^5 , and R^6 is a methoxymethyl group.

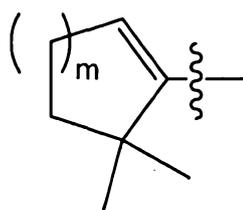
[0135] In some embodiments of the compound of formula I or I', A is a group of formula A' where the wavy line indicates the point of attachment and R^4 , R^5 , and R^6 are independently selected from H, F, OH, -O-(C₁-C₃)alkyl, (C₁-C₆)alkyl and (C₂-C₆)alkenyl, and two of R^4 , R^5 , and R^6 are other than H; or two or three of R^4 , R^5 , and R^6 join together to form an optionally substituted saturated or partially unsaturated 3-8 membered monocyclic or bicyclic ring. In some such embodiments, R^4 , R^5 , and R^6 are independently selected from H, OH, OMe, OEt, (C₁-C₆)alkyl, and (C₂-C₆)alkenyl groups and at least two of R^4 , R^5 , and R^6 are (C₁-C₄)alkyl groups. In some such embodiments, all three of R^4 , R^5 , and R^6 are independently selected from (C₁-C₄)alkyl groups. In some such embodiments, two of R^4 , R^5 , and R^6 are methyl groups. In some such embodiments, each of R^4 , R^5 , and R^6 is a methyl group. In other embodiments, R^4 , R^5 , and R^6 are independently selected from H, (C₁-C₄)alkyl groups, or a substituted (C₁-C₄)alkyl group selected from (C₁-C₄)haloalkyl groups, (C₁-C₄)perhaloalkyl groups, or (C₁-C₄)alkoxy(C₁-C₄)alkyl groups. In some such embodiments, at least one of R^4 , R^5 , and R^6 is a CF₃ group. In other embodiments at least one of R^4 , R^5 , and R^6 is a methoxymethyl group. In other embodiments, at least one of R^4 , R^5 , and R^6 is selected from OH, methoxy, or is ethoxy. In some such embodiments one of R^4 , R^5 , and R^6 is a methoxy. In other such embodiments one of R^4 , R^5 , and R^6 is OH. In other such embodiments one of R^4 , R^5 , and R^6 is ethoxy.

[0136] In some embodiments of the compound of formula I or I' where A is a group of formula A', two of R^4 , R^5 , and R^6 , together with the C atom to which they are attached, join to form a 3-8 or 3-7 membered ring, and the other of R^4 , R^5 , and R^6 is selected from H, an unsubstituted (C₁-C₄)alkyl, or a substituted (C₁-C₄)alkyl. In some

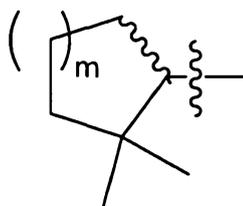
embodiments the ring is a carbocyclic ring which may be a fully saturated cycloalkyl ring. In some such embodiments, the 3-8 membered ring is a 5-7 membered ring, a 3-6 membered ring, or a 3-5 membered ring. Examples of such rings include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl rings. In some such embodiments, two of R⁴, R⁵, and R⁶ join to form a cyclopropyl ring. In some such embodiments, the other of R⁴, R⁵, and R⁶ is H. In some embodiments two of R⁴, R⁵, and R⁶, together with the C atom to which they are attached, join to form an optionally substituted saturated or partially unsaturated 3-8 or 3-7 membered ring which may be monocyclic or bicyclic, and the other of R⁴, R⁵, and R⁶ is selected from H, an unsubstituted (C₁-C₄)alkyl, or a substituted (C₁-C₄)alkyl. In some embodiments the ring only includes carbon ring members. In some such embodiments, the ring includes 0 or 1 double bonds between ring members. In some such embodiments, the 3-7 membered ring is a 3-6, or a 3-5 membered ring. Examples of such rings include cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cycloheptenyl rings. In some such embodiments, two of R⁴, R⁵, and R⁶ join to form an optionally substituted cyclopropyl ring. In some such embodiments, the other of R⁴, R⁵, and R⁶ is H. In some such embodiments, two of R⁴, R⁵, and R⁶ join to form an optionally substituted cyclopentenyl, cyclohexenyl, or cycloheptenyl ring. In some such embodiments, the other of R⁴, R⁵, and R⁶ is H. In some embodiments all three of R⁴, R⁵, and R⁶, together with the C atom to which they are attached, join to form an optionally substituted saturated or partially unsaturated 3-8 membered ring bicyclic ring system. For example, in some embodiments, A may comprise an adamantyl or another bicyclic ring system such as, but not limited to bicyclo[3.2.1]octane, bicyclo[2.2.1]heptane, and the like. In some such embodiments the ring only includes carbon ring members. In some such embodiments, the ring includes 0 or 1 double bonds between ring members. In some embodiments, A is a branched chain (C₄-C₈)alkyl group such as a t-butyl group. In other such embodiments, A is an optionally substituted (C₅-C₇)cycloalkyl group or an optionally substituted (C₅-C₇)cycloalkenyl group. In some such embodiments, the (C₅-C₇)cycloalkyl group or the (C₅-C₇)cycloalkenyl group are substituted with 1, 2, 3, or 4 methyl groups. In some other such embodiments, A has the formula



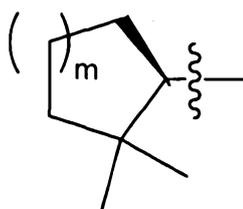
wherein m is 1, 2, or 3, and the dashed line indicates a single or double bond. In some such embodiments, A has the formula



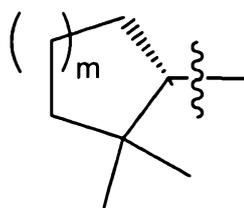
wherein m is 1, 2, or 3. In other such embodiments, A has the formula



wherein m is 1, 2, or 3 and the wavy line indicates that the compound has the R stereochemistry, the S stereochemistry, or a mixture of the R and S stereochemistry with respect to the carbon attached to the rest of the molecule. In some such embodiments, A has the formula

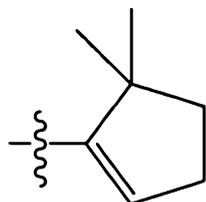


wherein m is 1, 2, or 3. In other embodiments, A has the formula

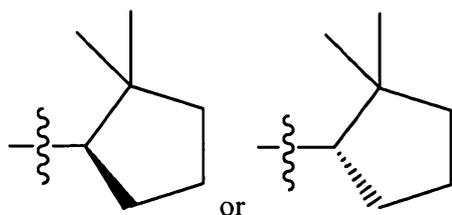


wherein m is 1, 2, or 3. In some embodiments, A is an $-OR^{4a}$ group. In some such embodiments, R^{4a} is selected from a methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, t-butyl, or an isomer thereof. In some embodiments, R^{4a} is selected from such an alkyl group that is substituted. For example, in some embodiments, R^{4a} may be a trihaloalkyl group such as a CF_3 group or another perhaloalkyl group.

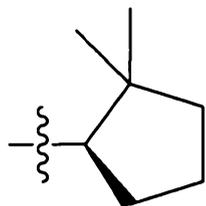
[0137] In some embodiments, A is



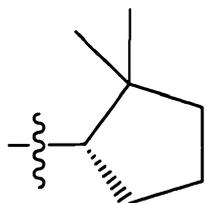
[0138] In some embodiments, A is selected from



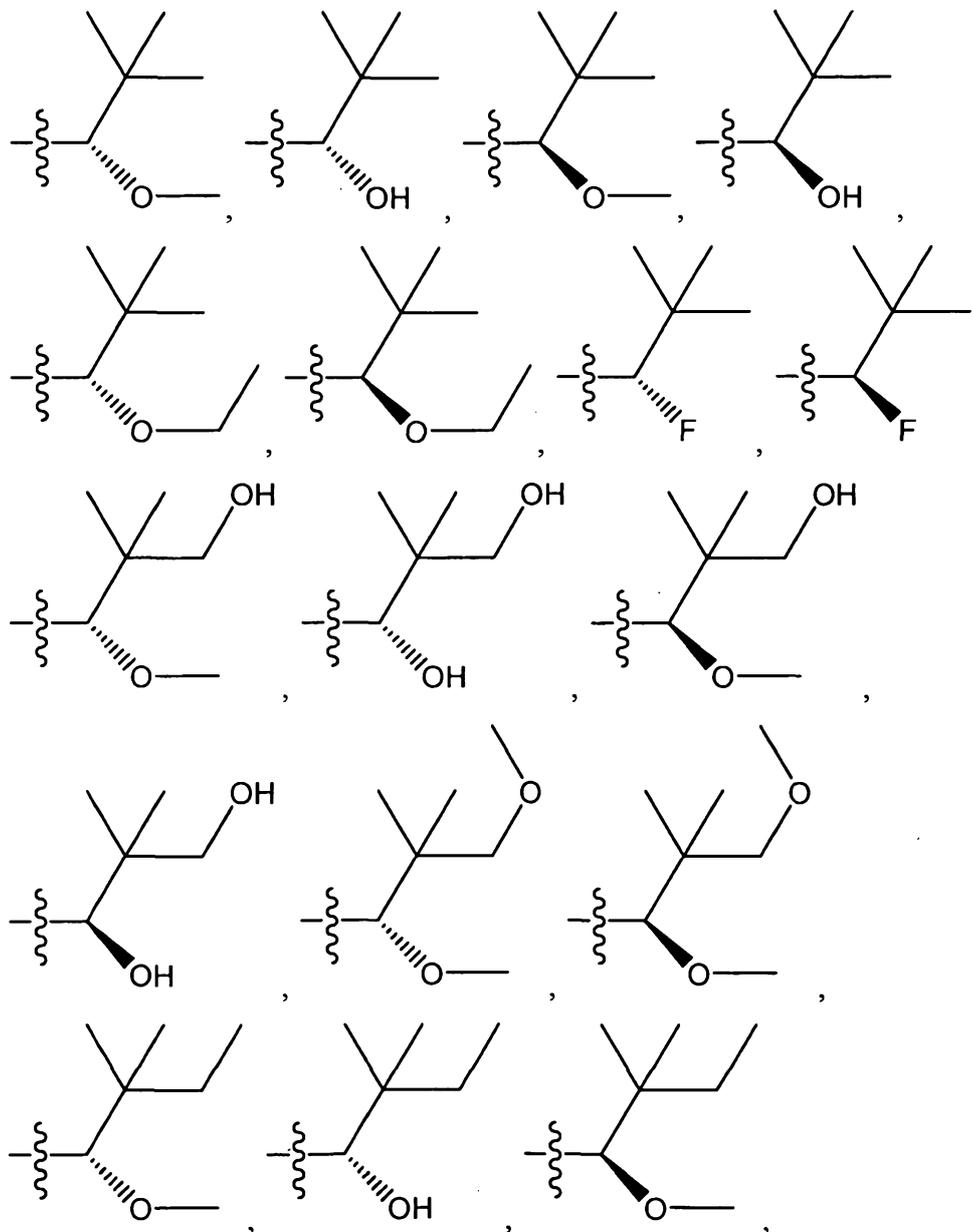
[0139] In some embodiments, A is

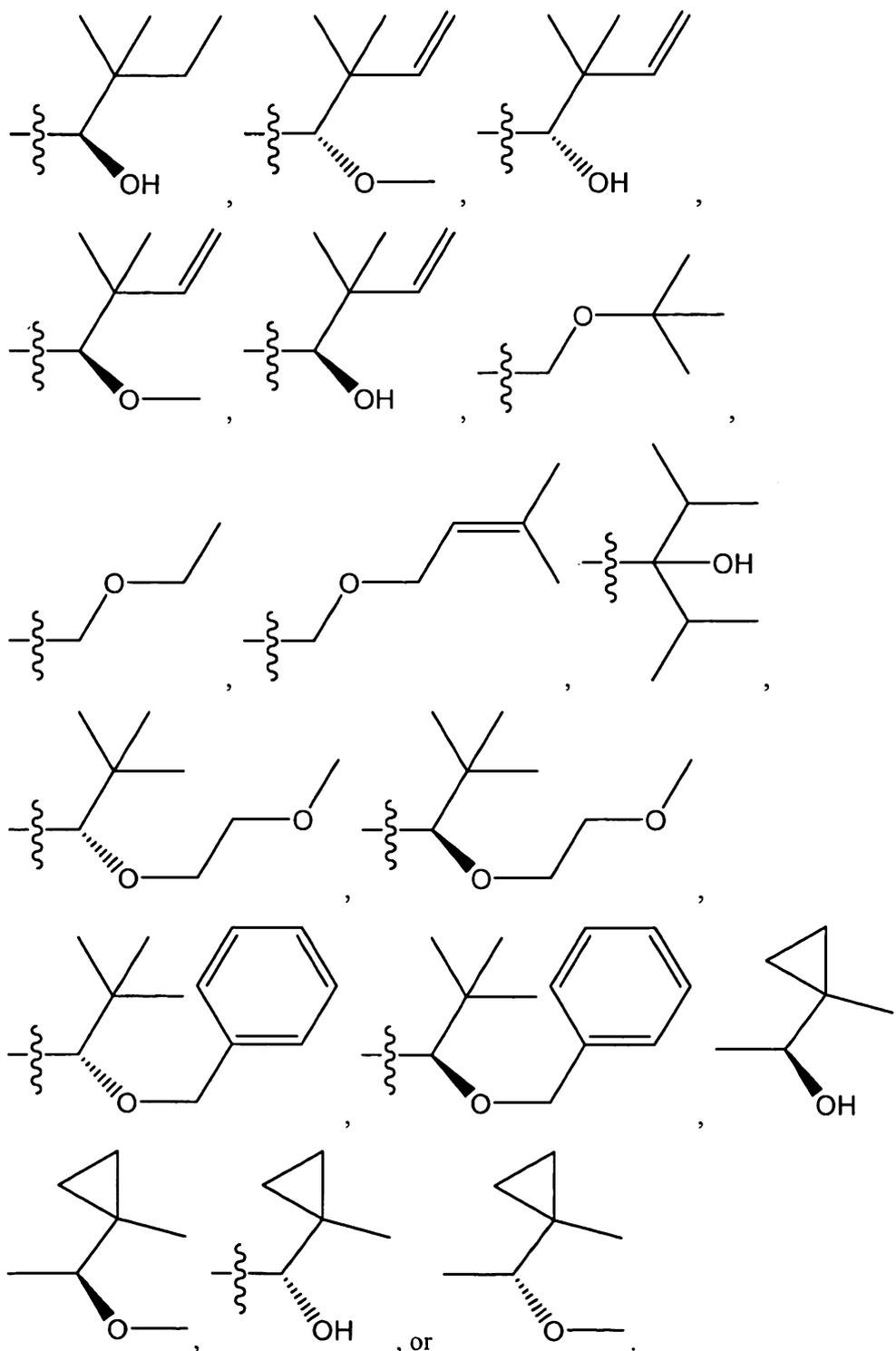


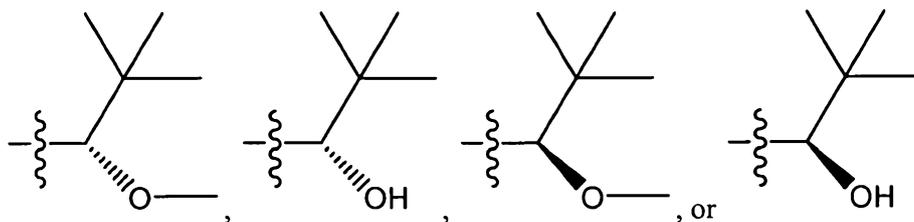
[0140] In some embodiments, A is



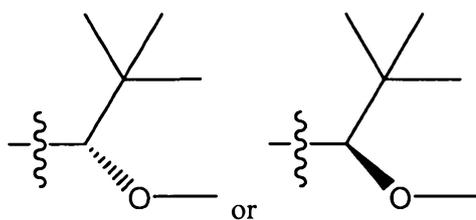
[0141] In some embodiments of the compound of formula I or I', A is a (C₁-C₁₂)alkyl or is a (C₂-C₁₂)alkenyl group and the (C₁-C₁₂)alkyl or the (C₂-C₁₂)alkenyl group is substituted with at least one A" group where A" is selected from -F, -OH, -O-(C₁-C₄)alkyl, -O(C₁-C₄)alkyl-aryl, -O(C₂-C₈)alkenyl, or -O-(C₁-C₄)alkyl-O-(C₁-C₄)alkyl. Therefore, in some embodiments A is selected from any one or all of:



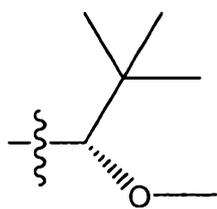




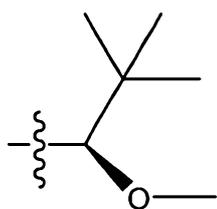
[0143] In some embodiments, A is selected from



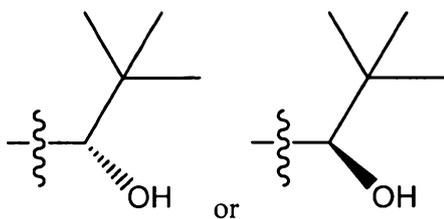
[0144] In some embodiments, A is



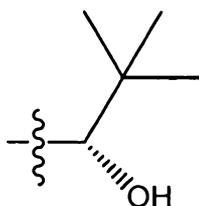
[0145] In some embodiments, A is



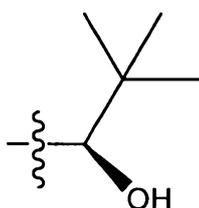
[0146] In some embodiments, A is selected from



[0147] In some embodiments, A is



[0148] In some embodiments, A is



[0149] In some embodiments of the compound of formula I or I', R² is F or butoxy. In some such embodiments, R² is F whereas in other such embodiments, R² is butoxy. In still other embodiments, R² is propoxy, pentoxy, or hexoxy. In still further embodiments, R² is selected from F or (C₃-C₄) alkoxy. In some embodiments, R² is a -CF₃ group.

[0150] In some embodiments of the compound of formula I or I', R³ is methoxy or ethoxy. In some such embodiments, R³ is methoxy.

[0151] In some embodiments of the compound of formula I or I', R³ is a substituted or unsubstituted -O(C₁-C₂)alkyl group. In some such embodiments, R³ is a -OCHF₂ group.

[0152] In some embodiments of the compound of formula I or I', X is O. In other embodiments, X is S.

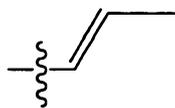
[0153] In some embodiments of the compound of formula I or I', R⁷ and R⁸ are both H. In some embodiments one of R⁷ and R⁸ is H and the other of R⁷ and R⁸ is methyl. Therefore, in some embodiments R⁷ and R⁸ are independently selected from H and methyl.

[0154] In some embodiments of the compound of formula I or I', R⁹ and R¹⁰ are both H. In other embodiments, R⁹ and R¹⁰ are selected from H and methyl. In some such embodiments, one of R⁹ and R¹⁰ is H and the other of R⁹ and R¹⁰ is methyl.

[0155] In some embodiments of the compound of formula I or I', R¹ is selected from (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, heterocyclyl, or heteroaryl. In some such embodiments, R¹ is a (C₁-C₄) alkyl. In some such embodiments, R¹ is a methyl, ethyl, propyl, or butyl group. In some such embodiments, R¹ is a methyl, ethyl, or propyl.

In some such embodiments, R^1 is a propyl group. In some embodiments, R^1 is a (C_3 - C_6)alkyl group that is a cycloalkyl group such as cyclopropyl, cyclobutyl, or cyclopentyl group. In some embodiments, R^1 is a CF_3 group. In other embodiments, R^1 is a $-CH_2CF_3$ group. In still other embodiments, R^1 is a $-CH_2CH_2CF_3$ group. In some embodiments, R^1 is a cyclopropyl group or a cyclobutyl group that is optionally substituted. In some such embodiments, R^1 is selected from a cyclopropyl group that is optionally substituted with one or two methyl groups. In other embodiments, R^1 is a cyclobutyl group that is optionally substituted with one or two methyl groups. In still other embodiments, R^1 is a cyclopropylmethyl ($-CH_2$ (cyclopropyl)) group. In yet other embodiments, R^1 is a cyclobutylmethyl ($-CH_2$ (cyclobutyl)) group. In some embodiments, R^1 is a $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-C(H)(CH_3)_2$, $-CH=CH_2$, $-C(CH_3)=CH_2$, $-CH_2C(H)=CH_2$, $-CF_3$, $-CH_2CH_2CF_3$, $-cyclopropyl$, $-cyclobutyl$, $-CH_2-cyclopropyl$, $-CH_2-cyclobutyl$, $-CH_2-O-CH_3$, $-CH=CHCH_2CH_3$, or $-CH_2CH(CH_3)_2$. In some such embodiments, R^{1a} is $-H$ whereas in other such embodiments, R^{1a} is $-CH_3$.

[0156] In some embodiments of the compound of formula I or I', R^1 is a cis (C_2 - C_6) alkenyl group whereas in other embodiments R^1 is a trans (C_2 - C_6) alkenyl group. In some embodiments, R^1 is a mixture of cis and trans (C_2 - C_6) alkenyl groups. In other embodiments, R^1 is a (C_2 - C_4) alkenyl group. In some embodiments R^1 is a cis (C_2 - C_4) alkenyl group whereas in other embodiments R^1 is a trans (C_2 - C_4) alkenyl group. In some embodiments, R^1 is a mixture of cis and trans (C_2 - C_4) alkenyl groups. In some embodiments, R^1 is selected from $-CH=CH_2$, $-CH=CH-CH_3$, $-CH=CH-CH_2-CH_3$, or $-CH_2-CH=CH_2$. In some such embodiments, R^1 is $-CH_2-CH=CH_2$. In some such embodiments, R^1 is $-CH=CH-CH_3$. In some such embodiments, R^1 has the formula

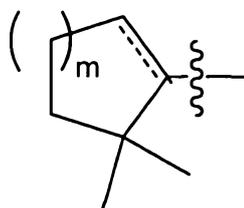


In other such embodiments, R^1 has the formula

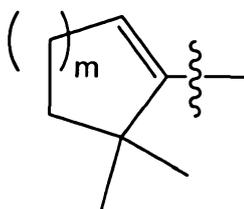


[0157] In some embodiments of the compound of formula I or I', R¹ is a (C₂-C₄) alkynyl. For example, in some embodiments, R¹ is -C≡C-CH₃.

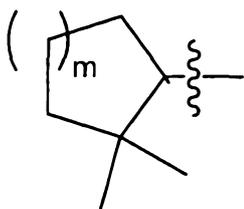
[0158] In some embodiments of the compound of formula I, G is CR^{11a}; J is CR^{11b}; L is CR^{11c}; K is CR^{11d}; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{12a}, R^{12b}, and R^{12c} are all H; R^{1a} is H; W is C-H; Y, is C-H; Z is C-H; R² is F; R³ is methoxy; R⁷ is H; R⁸ is H; R⁹ is H; R¹⁰ is H; X is O, and q is 1. In some such embodiments, A is a branched chain (C₄-C₈)alkyl group such as a t-butyl, -CH₂CH₂C(CH₃)₃, -CH₂CH₂CH(CH₃)₂, -CH(CH₃)(cyclopropyl), or -C(CH₃)₂CH₂CH₂CH₃ group. In some such embodiments, A is a t-butyl group. In other such embodiments, A is an optionally substituted (C₅-C₇)cycloalkyl group or an optionally substituted (C₅-C₇)cycloalkenyl group. In some such embodiments, the (C₅-C₇)cycloalkyl group or the (C₅-C₇)cycloalkenyl group are substituted with 1, 2, 3, or 4 methyl groups. In some other such embodiments, A has the formula



wherein m is 1, 2, or 3, and the dashed line indicates a single or double bond. In some such embodiments, A has the formula



wherein m is 1, 2, or 3. In other such embodiments, A has the formula



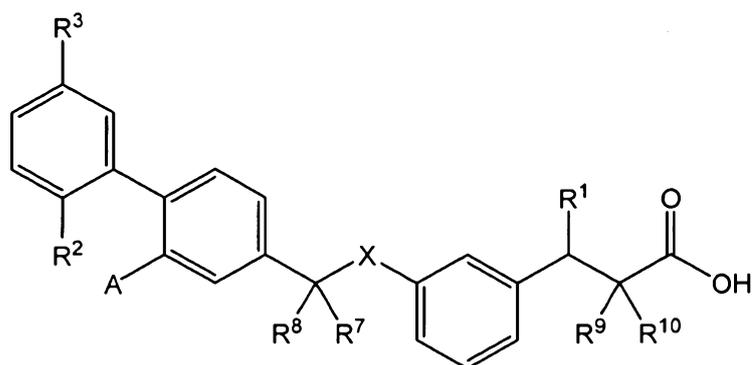
wherein m is 1, 2, or 3. In some such embodiments, A is a (C₄-C₁₀)alkenyl group. In some such embodiments, A is selected from -CH=CH-C(CH₃)₃, -CH=CH-CH₂CH₂CH₃, -CH=CH-cyclopropyl, or -CH=CH-cyclohexyl groups.

[0159] In some embodiments of the compound of formula **I**, G is CR^{11a}; J is CR^{11b}; L is CR^{11c}; K is CR^{11d}; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{12a}, R^{12b}, and R^{12c} are all H; R^{1a} is H; W is C-H; Y, is C-H; Z is C-H; R² is F; R³ is methoxy; R⁷ is H; R⁸ is H; R⁹ is H; R¹⁰ is H; X is O, q is 1, and A is -O-(C₁-C₁₂)alkyl, -O-(C₂-C₁₂)alkenyl, or -O-(C₁-C₄)alkyl-aryl. In some such embodiments, A is a -OCH₂-phenyl. In other embodiments, A is a -O-CF₃. In other such embodiments, A is a -O-(C₃-C₁₀)alkyl or -O-(C₃-C₁₀)alkenyl group. In other such embodiments, A is -O-(C₃-C₈)cycloalkyl optionally substituted with 1 or 2 methyl groups. In some such embodiments, A is an unsubstituted -O-(C₃-C₈)cycloalkyl group. In some such embodiments, A is a cyclopropyloxy, a cyclobutyloxy, a cyclopentyloxy, a cyclohexyloxy, or a cycloheptyloxy group. In some embodiments, A is a -O-CH₂CH₂CH₃, -O-CH₂CH₂CH₂CH₃, -O-CH₂CH₂CH₂CH₂CH₃, -O-CH(CH₃)₂, or -O-CH₂CH(CH₃)₂.

[0160] In some embodiments of the compound of formula **I** or **I'**, R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{12a}, R^{12b}, and R^{12c} are all H; R^{1a} is H; W is C-H; Y, is C-H; Z is C-H; R⁷ is H; R⁸ is H; R⁹ is H; R¹⁰ is H; X is O; and A is -OR^{4a}. In some such embodiments, q is 1.

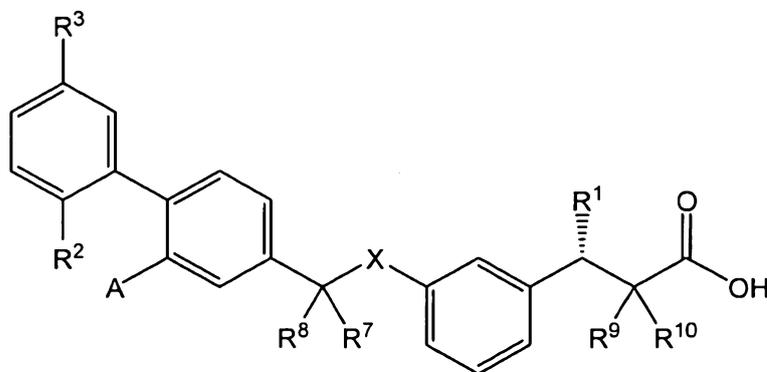
[0161] In some embodiments of the compound of formula **I** or **I'**, G is CR^{11a}; J is CR^{11b}; L is CR^{11c}; K is CR^{11d}; R^{11a} is H or F; R^{11b}, R^{11c}, and R^{11d} are H; R^{1a} is H; W is C-H; Z is C-H; R² is F; R³ is methoxy; R⁷ is H; R⁸ is H; R⁹ is H; R¹⁰ is H; X is O; q is 1; and two of R^{12a}, R^{12b}, and R^{12c} are H and the other of R^{12a}, R^{12b}, and R^{12c} is F. In some such embodiments, R^{11a} is H whereas in other such embodiments, R^{11a} is F.

[0162] In some embodiments, the compound of formula **I** or **I'** is a compound of formula **II** or a pharmaceutically acceptable salt, stereoisomer, C₁-C₆ alkyl ester, or mixture thereof. The compound of formula **II** has the following structure where each of the variables has any of the values of any of the embodiments described herein:



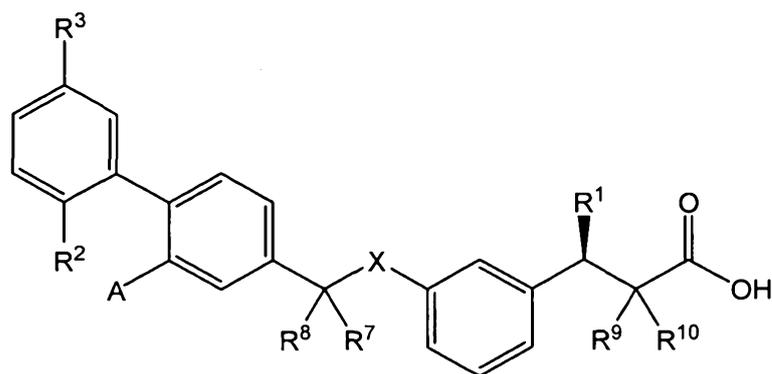
II.

[0163] In some embodiments, the compound of formula II is a compound of formula II' or a pharmaceutically acceptable salt, stereoisomer, C₁-C₆ alkyl ester, or mixture thereof. The compound of formula II' has the following structure where each of the variables has any of the values of any of the embodiments described herein:



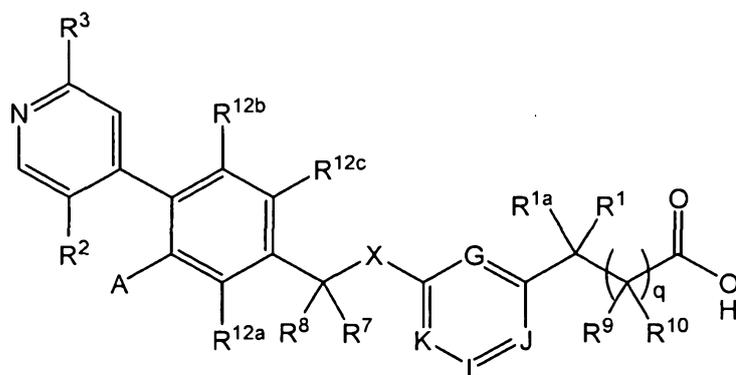
II'.

[0164] In some embodiments, the compound of formula II is a compound of formula II'' or a pharmaceutically acceptable salt, stereoisomer, C₁-C₆ alkyl ester, or mixture thereof. The compound of formula II'' has the following structure where each of the variables has any of the values of any of the embodiments described herein:



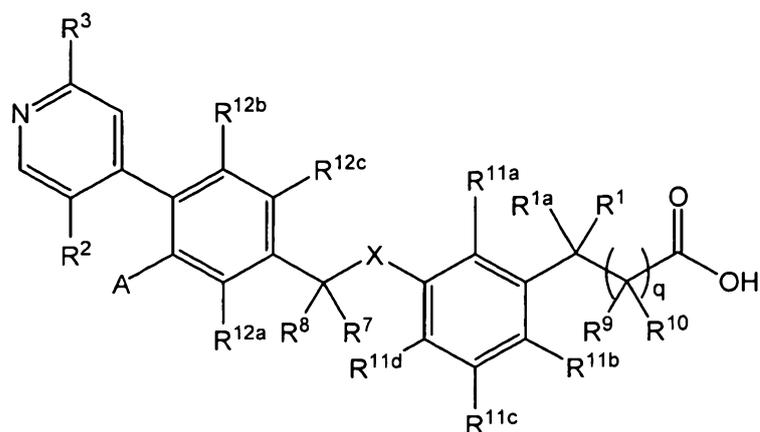
II'.

[0165] In some embodiments of the compound of formula I, W and Z are CH and Y is N such that the compound of formula I has the formula III or is a pharmaceutically acceptable salt, stereoisomer, C₁-C₆ alkyl ester, or mixture thereof. The compound of formula III has the following structure where each of the variables has any of the values of any of the embodiments described herein:



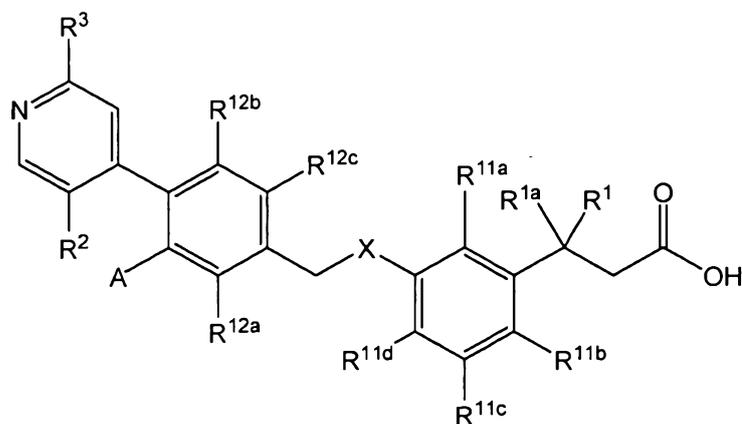
III.

[0166] In some embodiments, the compound of formula III is a compound of formula III' or a pharmaceutically acceptable salt, stereoisomer, C₁-C₆ alkyl ester, or mixture thereof. The compound of formula III' has the following structure where each of the variables has any of the values of any of the embodiments described herein:



III'.

[0167] In some embodiments, the compound of formula III is a compound of formula III'' or a pharmaceutically acceptable salt, stereoisomer, C₁-C₆ alkyl ester, or a mixture thereof. The compound of formula III'' has the following structure where each of the variables has any of the values of any of the embodiments described herein:



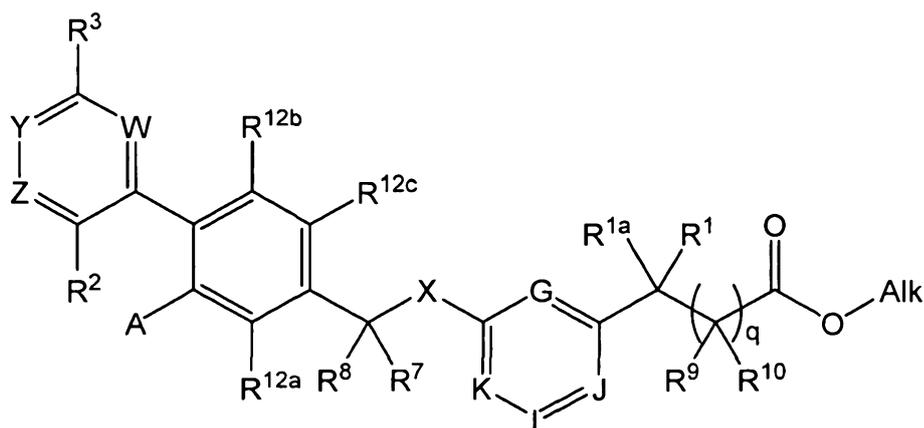
III''.

[0168] In some embodiments of the compound of formula III, formula III', or formula III'', R^{11a} is selected from H or F. In some such embodiments, R^{11a} is H whereas in other such embodiments R^{11a} is F. In some embodiments, R^{11b}, R^{11c}, and R^{11d} are each H. In still other embodiments, R^{11a} is F, R^{11b} is H, R^{11c} is H, and R^{11d} is H whereas in other embodiments R^{11a} is H, R^{11b} is H, R^{11c} is H, and R^{11d} is H. In still other such embodiments R² is F. In still other such embodiments, R³ is methoxy (-OCH₃). In still further such embodiments, one of R^{12a}, R^{12b}, and R^{12c} is F and the other two of R^{12a}, R^{12b}, and R^{12c} are H. In some such embodiments, R^{12c} is F, R^{12a} is H, and R^{12b} is H. In other

embodiments, each of R^{12a} , R^{12b} , and R^{12c} is H. In some embodiments, X is selected from O or S. Therefore, in some embodiments, X is O whereas in other embodiments, X is S.

[0169] In some embodiments, the compound of formula I is selected from a group that includes each, all, or any one of the compounds in any of the tables or is a pharmaceutically acceptable salt, or C_1 - C_6 alkyl ester thereof. In some such embodiments where the compound has a chiral center, the compound exists as a single enantiomer whereas in other embodiments, the compound is a mixture of enantiomers of the compounds shown above. In some such embodiments, the compound of formula I is one of the compounds in any of the tables or is a pharmaceutically acceptable salt, or C_1 - C_6 alkyl ester thereof. In other embodiments, the compound is an enantiomer or diastereomer of one of the compounds in any of the tables or is a pharmaceutically acceptable salt, or C_1 - C_6 alkyl ester thereof.

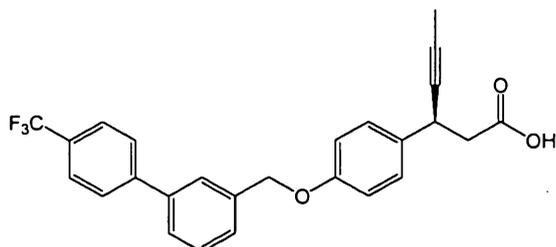
[0170] In some embodiments, the compound of formula I is a C_1 - C_6 alkyl ester. Such esters typically have the formula IE where each of the variables has any of the values set forth herein with respect to any of the embodiments, and Alk is a C_1 - C_6 alkyl group. In some such embodiments, Alk is a methyl or ethyl group such that the compound is a methyl or ethyl ester.



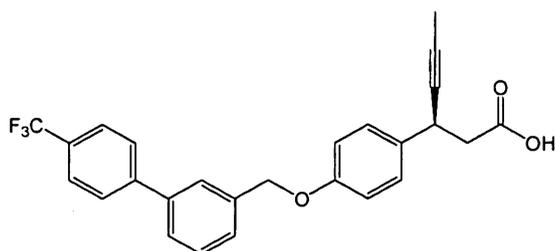
IE.

[0171] In some embodiments, the compound is selected from any of those in any of the tables. Furthermore, in some embodiments, the compound of formula I has a variable corresponding to any of the groups in the compounds of any of the tables. For example, if a compound in any of the tables has a group corresponding to the A group, then in some embodiments of the compound of formula I, the A group will correspond to that set forth in the compound(s) in any of the tables.

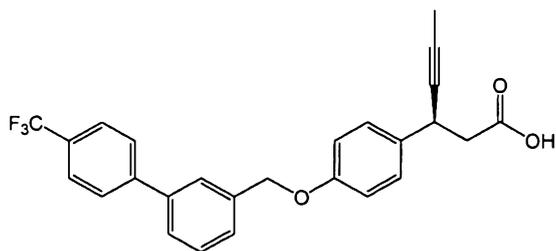
[0172] In some embodiments, the compound of any of the embodiments described herein does not displace a compound of the following formula that is bound to the GPR40 receptor



[0173] In some embodiments, the compound of any one of the embodiments described herein binds to a different site on the GPR40 receptor than does a compound of formula



[0174] In one aspect, the invention provides a compound that binds to a different site on the GPR40 receptor than does the following compound



wherein the compound is a synthetic compound that does not occur naturally in the body of an animal. In some such embodiments, the compound comprises a biphenyl group. In other such embodiments, the compound comprises a biphenyl group and a phenyl group that is not part of the biphenyl group. In some such embodiments, the compound further comprises a carboxylic acid group or a salt of such a group. In still other such compounds, the phenyl group that is not part of the biphenyl group is meta substituted.

[0175] In some embodiments, the compound of any of the embodiments is a salt. In other embodiments, the compound of any of the embodiments is a C₁-C₆ alkyl ester. In

some such embodiments, the C₁-C₆ alkyl ester is a C₁-C₆ alkyl ester such as a methyl, ethyl, propyl, butyl, isopropyl, pentyl, or hexyl ester. In other embodiments, the C₁-C₆ alkyl ester is a methyl, ethyl, propyl, or butyl ester. In some such embodiments, the ester is a methyl or ethyl ester.

[0176] In some embodiments, the compound comprises a stereomerically pure S-enantiomer. In other embodiments, the compound comprises a stereomerically pure R-enantiomer. In yet other embodiments, the compound comprises a mixture of S- and R-enantiomers.

[0177] In another aspect, the invention provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier, diluent, or excipient, and a compound of any of the embodiments of the invention.

[0178] In another aspect, a compound of any of the embodiments described herein is used to prepare a medicament.

[0179] In yet another aspect, the invention provides a therapeutic composition that includes a compound of any of the embodiments and a second therapeutic agent as a combined preparation for simultaneous, separate, or sequential use in the treatment of a disease or condition mediated by GPR40. In some such embodiments, the disease or condition is type II diabetes. In some embodiments, the second therapeutic agent is selected from metformin, a thiazolidinedione, or a DPP-IV inhibitor. In some embodiments, the compound of any of the embodiments described herein and the second therapeutic agent are provided as single composition. In other embodiments, the compound of any of the embodiments described herein and the second therapeutic agent are provided separately as parts of a kit.

[0180] In some embodiments, the invention provides a compound of any of the embodiments described herein for use as a medicament.

[0181] In some embodiments, the invention provides a compound of any of the embodiments described herein for use in modulating GPR40.

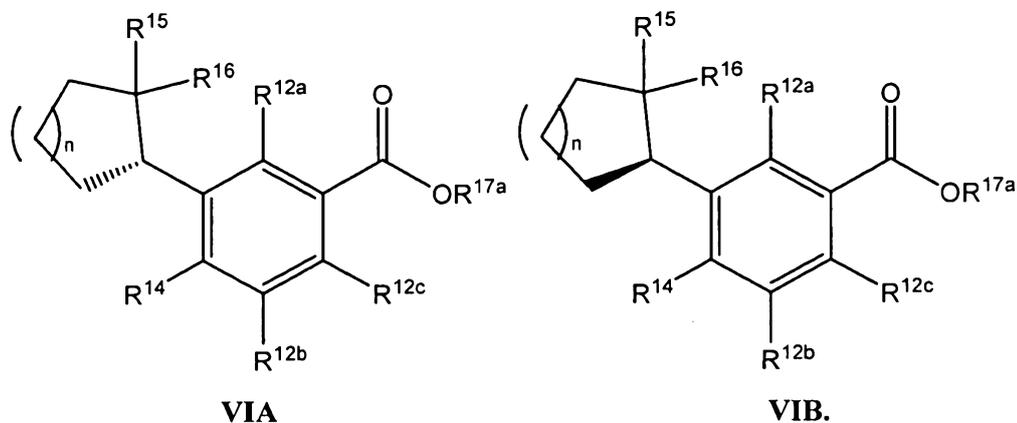
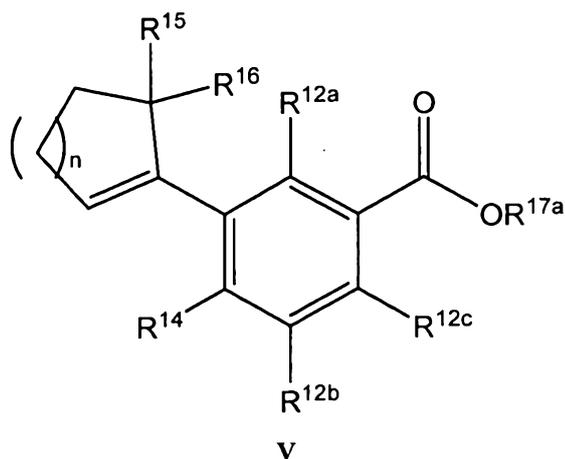
[0182] In some embodiments, the invention provides a compound of any of the embodiments described herein for use in treating a disease or condition selected from type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic

disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer, or edema. In some such embodiments, the compound is used for treating type II diabetes.

[0183] The compounds of the invention have been found to stimulate GLP-secretion. Cells contacted with compounds of the invention have been found to increase GLP-1 secretion. Therefore, in some embodiments, the invention provides a method of stimulating GLP-1 secretion by cells. Such methods typically include contacting a cell capable of producing GLP-1 with a compound of any of the embodiments set forth herein. Administration of the compounds of the invention to subjects has also been found to provide increased levels of GLP-1 in the blood plasma of such subjects. Therefore, in some embodiments, a compound of any of the embodiments described herein may be used to stimulate GLP-1 secretion and increase the blood plasma level of GLP-1 in a subject. In some such embodiments, the compounds of the invention both stimulate GLP-1 secretion and activate GPR40. Therefore, in some embodiments, the compounds of the invention both stimulate GLP-1 secretion and display incretin effect by activating GPR40.

[0184] In some embodiments, the invention further provides a method for increasing GLP-1 levels in the blood plasma of a subject. Such methods typically include administering a compound of any of the embodiments to a subject. In some such embodiments, the subject is a diabetic patient. In other such embodiments, the subject is an obese patient. The compounds of the invention may be administered in the fasted or non-fasted state. Therefore, in some embodiments, a compound of any of the embodiments is administered to a subject prior to a meal. In some such embodiments, the compound is administered 2 hours, 1 hour, 30 minutes, or 15 minutes before a meal. In other embodiments, a compound of any of the embodiments set forth herein is administered to a subject during a meal. In other embodiments, a compound of any of the embodiments described herein is administered to a subject within 2 hours, within 1 hour, within 30 minutes, or within 15 minutes of a meal.

[0185] In another aspect the invention provide a process for hydrogenating a compound of formula **V**, the method comprising: (a) reacting a compound of formula **V** with H_2 in the presence of a transition metal or a transition metal complex to form a compound of formula **VIA**, a compound of formula **VIB** or mixture of the compound of formula **VIA** and the compound of formula **VIB**. The compounds of formula **V**, **VIA**, and **VIB** have the following structures:



wherein,

R^{12a} is selected from -H, halo, a $-(C_1-C_6)$ alkyl group, or a $-O-(C_1-C_6)$ alkyl group;

R^{12b} is selected from -H, halo, a $-(C_1-C_6)$ alkyl group, or a $-O-(C_1-C_6)$ alkyl group;

R^{12c} is selected from -H, halo, a $-(C_1-C_6)$ alkyl group, or a $-O-(C_1-C_6)$ alkyl group;

R^{14} is -H or -OH;

R^{15} is selected from -H, or a $-(C_1-C_6)$ alkyl group;

R^{16} is selected from -H, or a $-(C_1-C_6)$ alkyl group;

R^{17a} is a $-(C_1-C_6)$ alkyl group; and

the subscript n is 1, 2, or 3;

wherein at least one of R^{15} or R^{16} is a $-(C_1-C_6)$ alkyl group.

[0186] In another aspect, the invention provides a compound of formula **V**, **VIA**, and/or **VIB**. In such an aspect, the variables have the definitions provided herein with respect to the process for hydrogenating a compound of formula **V**. In various

embodiments of this aspect, the variables have any of the definitions provided with respect to any of the embodiments of the process for hydrogenating a compound of formula V. For example, in some embodiments, R¹⁴ is OH. In other such embodiments, R¹⁵ and R¹⁶ are both methyl groups.

[0187] In some embodiments of the process for hydrogenating the compound of formula V, the transition metal or transition metal complex comprises palladium, platinum, nickel, or rhodium. For example, the reduction may be accomplished using palladium on carbon, Raney nickel, PtO₂ or various rhodium compounds. In some such embodiments, the transition metal or transition metal complex is palladium, and in some such embodiments is palladium on carbon. Various supported catalysts known to those skilled in the art may be used in conjunction with this process.

[0188] In some embodiments of the process for hydrogenating the compound of formula V, the process is an enantioselective process. In such embodiments, the method includes reacting a compound of formula V with H₂ in the presence of a transition metal or a transition metal complex and a phosphine ligand to form a compound of formula VIA, a compound of formula VIB, or a mixture of the compound of formula VIA and the compound of formula VIB. In such embodiments, the phosphine ligand comprises at least one chiral center.

[0189] In some embodiments of the process for hydrogenating a compound of formula V, R¹⁴ is -OH.

[0190] In some embodiments of the process for hydrogenating a compound of formula V, R¹⁵ and R¹⁶ are both -CH₃.

[0191] In some embodiments of the process for hydrogenating a compound of formula V, the subscript n is 1.

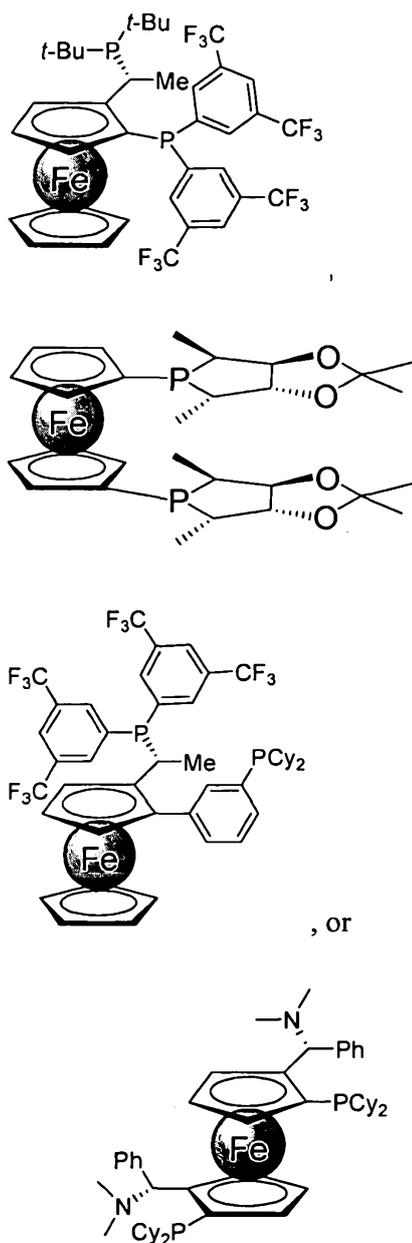
[0192] In some embodiments of the process for hydrogenating a compound of formula V, R^{12b} and R^{12c} are both -H.

[0193] In some embodiments of the process for hydrogenating a compound of formula V, R^{12a} is H or halo. Thus, in some embodiments R^{12a} is H whereas in other embodiments, R^{12a} is F.

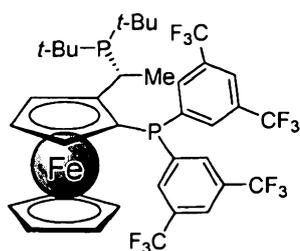
[0194] In some embodiments of the process for hydrogenating a compound of formula V, the transition metal or the transition metal complex comprises rhodium. For example, in some such embodiments, the transition metal complex is generated from

$\text{Rh}(\text{COD})_2\text{BF}_4$, $\text{Rh}(\text{COD})_2\text{SbF}_6$, or $\text{Rh}(\text{NBD})_2\text{BF}_4$ where COD represents the 1,5-cyclooctadiene ligand and NBD represents the norbornadiene ligand.

[0195] In some embodiments of the process for hydrogenating a compound of formula V, the phosphine is a diphosphine. In some such embodiments, the diphosphine comprises a ferrocene group. In some such embodiments, the diphosphine is selected from



In some such embodiments, the diphosphine is



In other such embodiments, the diphosphine is an enantiomer of one of the compounds shown above.

[0196] In some embodiments of the process for hydrogenating a compound of formula V, the compound of formula V is reacted with H₂ at a pressure of from 15 to 1400 psi. In some such embodiments, the pressure ranges from 50 to 400 psi.

[0197] In some embodiments of the process for hydrogenating a compound of formula V, the compound of formula V is reacted with H₂ in a mixture comprising at least one solvent selected from an ethereal solvent, an ester solvent, an aromatic solvent, a halogenated hydrocarbon solvent, a ketone solvent, or a C₁-C₄ alcohol solvent. In some such embodiments, the at least one solvent comprises an ethereal solvent selected from tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, 1,2-diethoxyethane, tetrahydropyran, diethylether, dipropylether, or dibutylether. In other such embodiments, the at least one solvent comprises tetrahydrofuran. In other such embodiments, the at least one solvent comprises at least one of tetrahydrofuran, toluene, acetone, methyl ethyl ketone, ethanol, or methanol.

[0198] In some embodiments, the transition metal complex is mixed with the phosphine in a solvent prior to adding the compounds of formula V. In some such embodiments, the solvent is an ethereal solvent such as tetrahydrofuran, and the transition metal complex is selected from Rh(COD)₂BF₄, Rh(COD)₂SbF₆, or Rh(NBD)₂BF₄. In some such embodiments, the phosphine is a diphosphine comprising a ferrocenyl group such as one of those described herein.

[0199] In some embodiments of the process for hydrogenating a compound of formula V, the compound of formula I is reacted with H₂ at a temperature ranging from 15°C to 60°C. In some such embodiments, the temperature ranges from 20°C to 45°C.

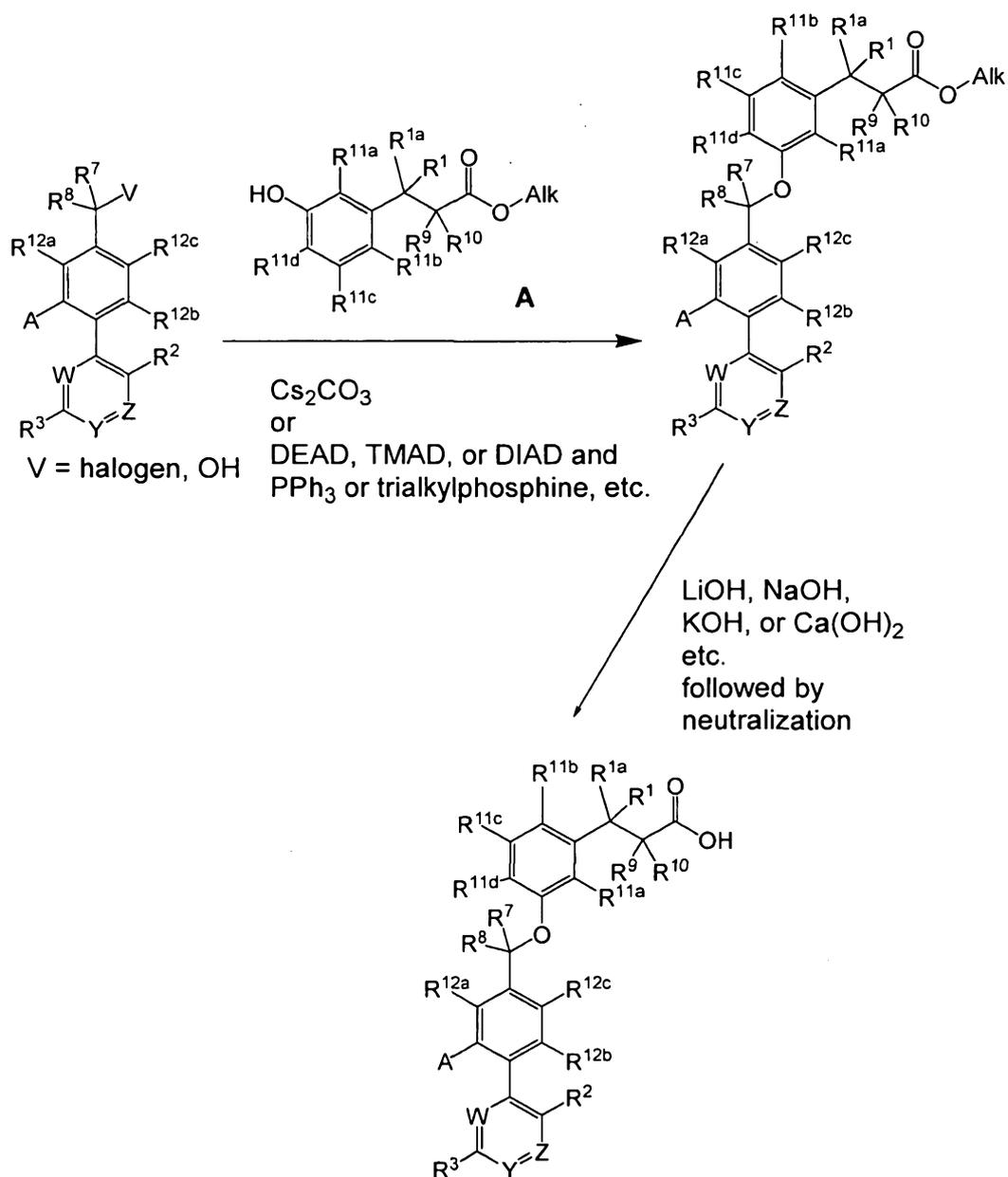
[0200] In some embodiments of the process for hydrogenating a compound of formula V, the enantiomeric excess of one of the products is greater than 50%, greater than 60%, greater than 75%, greater than 85%, greater than 90%, greater than 95%, or greater than 98%.

[0201] In some embodiments of the process for hydrogenating a compound of formula **V**, the conversion of the compound of formula **V** to the compound of formula **VIA**, the compound of formula **VIB**, or the mixture of the compound of formula **VIA** and the compound of formula **VIB** is greater than 50%, greater than 70%, greater than 80%, or greater than 95%.

6.2.2 Preparation of the Compounds

[0202] The compounds of the invention can be prepared by a variety of synthetic or semisynthetic techniques. Scheme 1 provides a general synthetic scheme for exemplary compounds of the invention utilizing ester **A** where the variables in Scheme 1 have any of the values described above with respect to any of the embodiments, **V** is a **OH** or a halogen such as, but not limited to a **Cl**, **Br**, or **I**, or sulfonate ester such as, but not limited to **OTs** (tosylate) or **OTf** (triflate); and **Alk** is a straight or branched chain alkyl group having from 1-8 carbon atoms. It will be understood that the phenolic **OH** group of **A** can be replaced with an **SH** and reacted with a compound where **V** is a halogen to produce the analogous **S**-containing derivative (**X = S**) to the compounds shown. The synthesis of various chloromethyl and hydroxymethyl biphenyl tail group compounds and phenol carboxylic acid head group compounds is described herein. Appropriate starting materials can be prepared by techniques known or apparent to those of skill in the art or the starting materials may be commercially available. One of skill in the art will understand that the synthetic routes can be modified to use different starting materials or alternative reagents and that suitable adjustments in conditions (e.g., temperatures, solvents, etc.) can be made to accomplish the desired transformations. One of skill in the art will recognize that protecting groups may be necessary for the preparation of certain compounds and will be aware of those conditions compatible with a selected protecting group. Examples of such protecting groups include, for example, those set forth in *Protective Groups in Organic Synthesis*, Greene, T. W.; Wuts, P. G. M., John Wiley & Sons, New York, N.Y., (3rd Edition, 1999). Accordingly, the exemplary methods and the examples described herein are illustrative of the present invention and are not to be construed as limiting the scope thereof.

Scheme 1



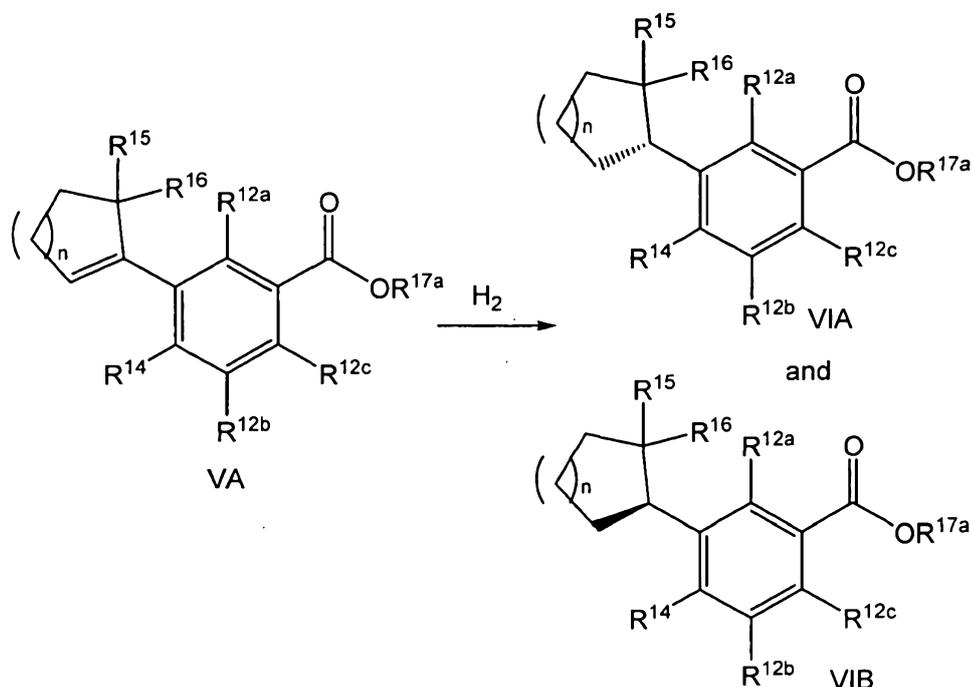
[0203] Certain compounds of the invention that include a compound with an A group that is a cycloalkyl ring possessing a chiral center can be produced using a hydrogenation process that has been discovered. For example, as shown in Scheme 2, a cycloalkenyl aryl compound such as a compound of formula V can be hydrogenated to provide the two cycloalkyl enantiomers VIA and VIB. Typically, the process includes:

(a) reacting a compound of formula **V** with H₂ in the presence of a transition metal or a transition metal complex to form a mixture of a compound of formula **VIA** and a compound of formula **VIB**. The compounds of formula **V**, **VIA**, and **VIB** have the structures shown below with respect to the enantioselective hydrogenation process.

[0204] In some embodiments of the process for hydrogenating the compound of formula **V**, the transition metal or transition metal complex comprises palladium, platinum, nickel, or rhodium. For example, the reduction may be accomplished using palladium on carbon, Raney nickel, PtO₂ or various rhodium compounds. Various supported catalysts known to those skilled in the art may be used in conjunction with this process.

[0205] Certain compounds of the invention that include a compound with an A group that is a cycloalkyl ring possessing a chiral center can also be produced using an enantioselective hydrogenation process that has been discovered. For example, as shown in Scheme 2, a cycloalkenyl aryl compound such as a compound of formula **V** can be hydrogenated to provide the two cycloalkyl enantiomers **VIA** and **VIB**. Typically, the method includes reacting a compound of formula **V** with H₂ in the presence of a transition metal or a transition metal complex and a phosphine ligand to form a compound of formula **VIA**, a compound of formula **VIB**, or a mixture of a compound of formula **VIA** and a compound of formula **VIB**.

Scheme 2



In the compounds of formula **VA**, **VIA**, and **VIB**, R^{12a} is selected from -H, halo, a $-(C_1-C_6)$ alkyl group, or a $-O-(C_1-C_6)$ alkyl group; R^{12b} is selected from -H, halo, a $-(C_1-C_6)$ alkyl group, or a $-O-(C_1-C_6)$ alkyl group; R^{12c} is selected from -H, halo, a $-(C_1-C_6)$ alkyl group, or a $-O-(C_1-C_6)$ alkyl group; R^{14} is -H or -OH; R^{15} is selected from -H, or a $-(C_1-C_6)$ alkyl group; R^{16} is selected from -H, or a $-(C_1-C_6)$ alkyl group; R^{17a} is a $-(C_1-C_6)$ alkyl group; and the subscript n is 1, 2, or 3. Generally, at least one of R^{15} or R^{16} is a $-(C_1-C_6)$ alkyl group. In some embodiments of the process for hydrogenating a compound of formula **V**, R^{15} and R^{16} are both $-CH_3$. In some embodiments of the process for hydrogenating a compound of formula **V**, the subscript n is 1. In some embodiments of the process for hydrogenating a compound of formula **V**, R^{12b} and R^{12c} are both -H.. In some embodiments of the process for hydrogenating a compound of formula **V**, R^{12a} is H or halo. Thus, in some embodiments R^{12a} is H whereas in other embodiments, R^{12a} is F.

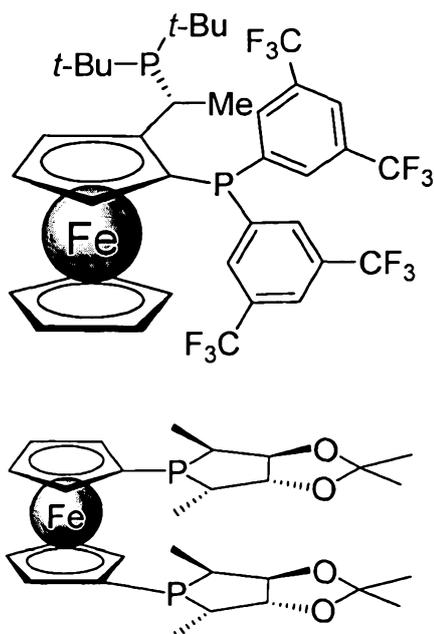
[0206] Various solvents and mixtures thereof can be used in the enantioselective hydrogenation process. Typical solvents for the reaction include ethereal solvents, ester solvents, aromatic solvents, halogenated hydrocarbon solvents, ketone solvents, and C_1-C_4 alcohol solvents. Examples of ethereal solvents include, but are not limited to cyclic and non-cyclic ethers including, but not limited to, tetrahydrofuran, 1,4-dioxane, 1,2-dimethoxyethane, 1,2-diethoxyethane, tetrahydropyran, diethylether, dipropylether, and

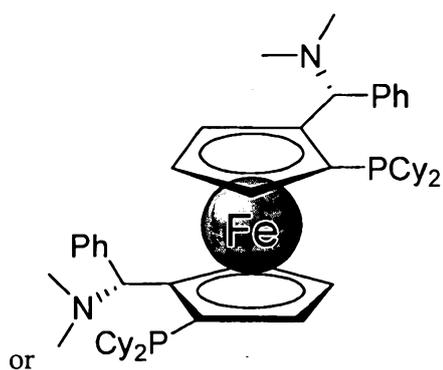
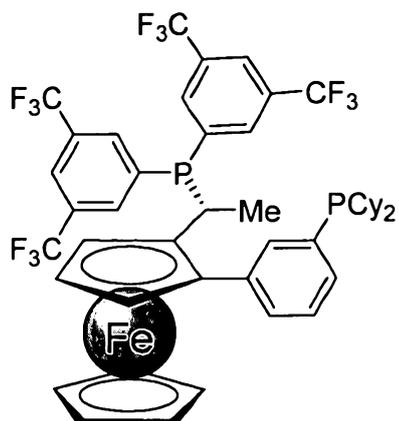
dibutylether. Tetrahydrofuran is an example of one solvent that has been found to function particularly well, but other solvents such as toluene, acetone, methyl ethyl ketone, dichloromethane, ethanol, and methanol may be employed in the reduction.

[0207] The enantioselective hydrogenation process may be conducted at various temperatures. For example, in some embodiments of the process for hydrogenating a compound of formula V, the compound of formula V is reacted with H₂ at a temperature ranging from 15°C to 60°C. In some such embodiments, the temperature ranges from 20°C to 45°C.

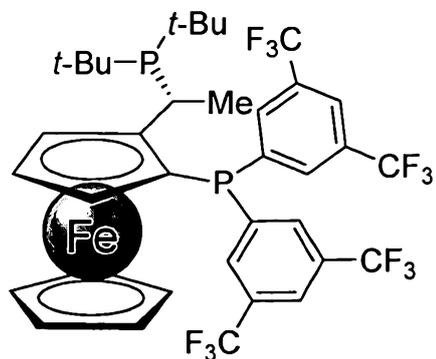
[0208] The enantioselective hydrogenation process may also be conducted at various pressures of H₂. For example, in some embodiments of the process for hydrogenating a compound of formula V, the compound of formula V is reacted with H₂ at a pressure of from 15 to 1400 psi. In some such embodiments, the pressure is from 50 to 400 psi whereas in other embodiments, the pressure ranges from 80 to 400 psi, from 100 to 400 psi, or from 100 to 200 psi.

[0209] In some embodiments of the process for hydrogenating a compound of formula V, the phosphine is a diphosphine. In some such embodiments, the diphosphine comprises a ferrocene group. Examples of diphosphines comprising a ferrocene group include, but are not limited to,





The following diphosphine has been found to be particularly effective. Therefore, in some embodiments, the diphosphine is



Enantiomers of the diphosphines shown above may be used to generate the other enantiomer as the majority product. Therefore, in some embodiments, the diphosphine is an enantiomer of one of those shown above.

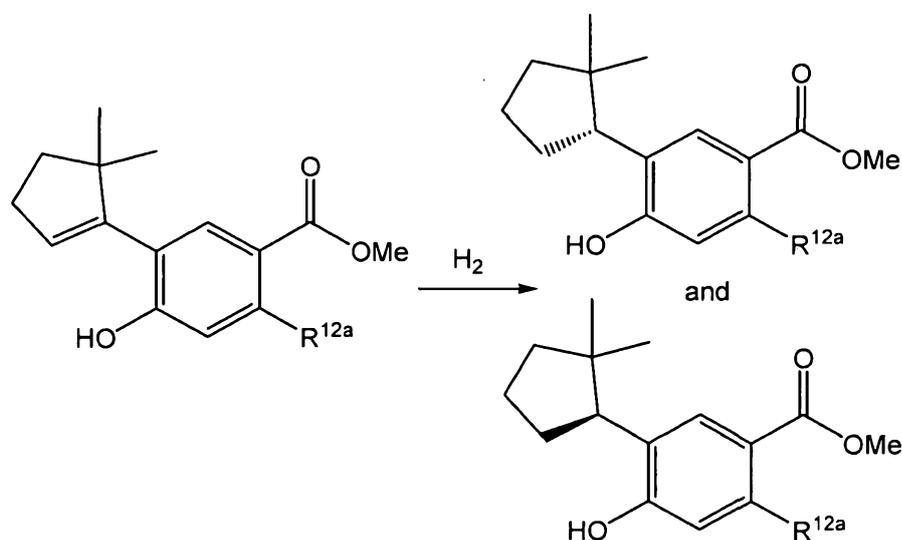
[0210] Various transition metals and transition metal complexes may be used to hydrogenate compounds of formula V. However, rhodium has been found to produce

particularly good results. Therefore in some embodiments for hydrogenating a compound of formula V, the transition metal or the transition metal complex comprises rhodium. For example, in some such embodiments, the transition metal or transition metal complex is generated from $\text{Rh}(\text{COD})_2\text{BF}_4$, $\text{Rh}(\text{COD})_2\text{SbF}_6$, or $\text{Rh}(\text{NBD})_2\text{BF}_4$.

[0211] Generally, the transition metal complex is mixed with the phosphine in a solvent prior to adding the compounds of formula V. In some such embodiments, the solvent is an ethereal solvent such as tetrahydrofuran, and the transition metal complex is selected from $\text{Rh}(\text{COD})_2\text{BF}_4$, $\text{Rh}(\text{COD})_2\text{SbF}_6$, or $\text{Rh}(\text{NBD})_2\text{BF}_4$. In some such embodiments, the phosphine is a diphosphine comprising a ferrocenyl group such as one of those described herein.

[0212] The enantioselective hydrogenation process has been found to provide compounds of formula VIA and VIB in good yield with excellent enantiomeric excess. Scheme 3 shows a general method for hydrogenating two compounds of formula V.

Scheme 3



[0213] Referring to Scheme 3, when R^{12a} is H, the cycloalkene was hydrogenated to provide the cyclopentyl compounds in good yield and with excellent enantiomeric excess. For example, a yield of 99% and a 99% enantiomeric excess was achieved after 2 hours at room temperature under 200 psi H_2 when the compound shown in Scheme 3 ($\text{R}^{12a} = \text{H}$) and triethylamine were added to the mixture prepared by mixing $\text{Rh}(\text{COD})_2\text{BF}_4$ and (R)-1-[(S)-2-(R)-(ditertbutylphosphino)ferrocenyl]ethyl-bis-(3,5-bis(trifluoromethyl)phenyl)phosphine in tetrahydrofuran. Good yields and enantiomeric excesses were also observed for compounds where R^{12a} is F. For example, a yield of 83%

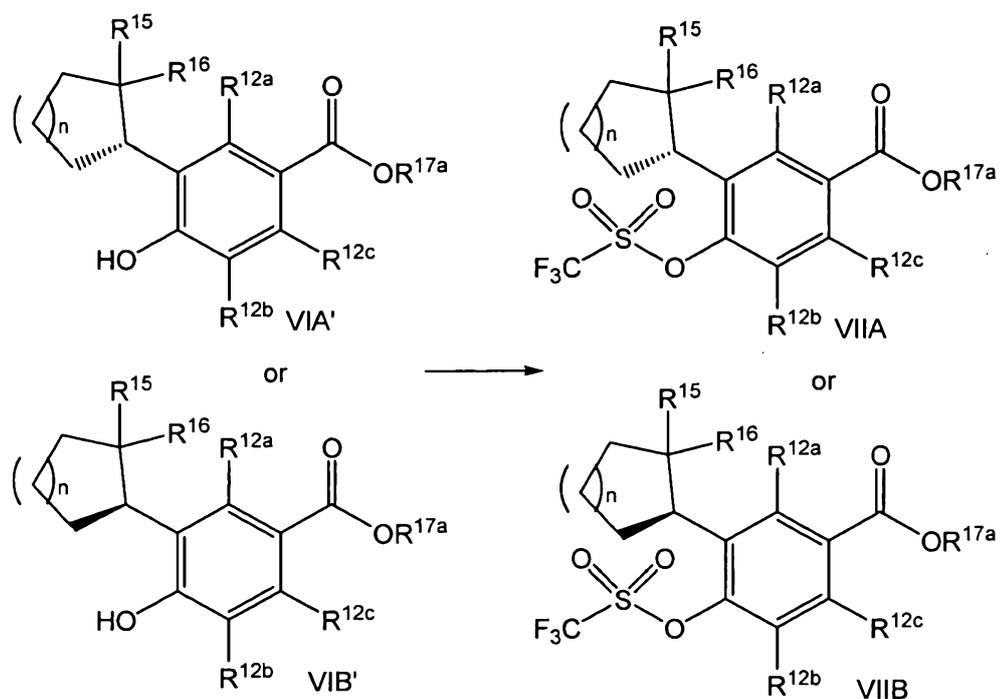
and a 99.3% enantiomeric excess was achieved after 2 hours at room temperature under 200 psi H₂ when the compound shown in Scheme 3 (R^{12a} = F) and triethylamine were added to the mixture prepared by mixing Rh(COD)₂BF₄ and (R)-1-[(S)-2-(R)-(ditertbutylphosphino)ferrocenyl]ethyl-bis-(3,5-bistrifluoromethylphenyl)phosphine in tetrahydrofuran. The presence of a trialkyl amine base such as triethylamine was found to slightly improve the enantiomeric excess in these reactions. While the trialkylamine was not required for the reaction to proceed with good enantioselectivity, it was found to improve the ee in cases where the starting material may have contained small amounts of impurities.

[0214] In some embodiments of the process for hydrogenating a compound of formula **V**, the enantiomeric excess of one of the products is greater than 50%, greater than 60%, greater than 75%, greater than 85%, greater than 90%, greater than 95%, or greater than 98%.

[0215] In some embodiments of the process for hydrogenating a compound of formula **V**, the conversion of the compound of formula **V** to the compound of formula **VIA**, the compound of formula **VIB**, or the mixture of the compound of formula **VIA** and the compound of formula **VIB** is greater than 50%, greater than 70%, greater than 80%, or greater than 95%.

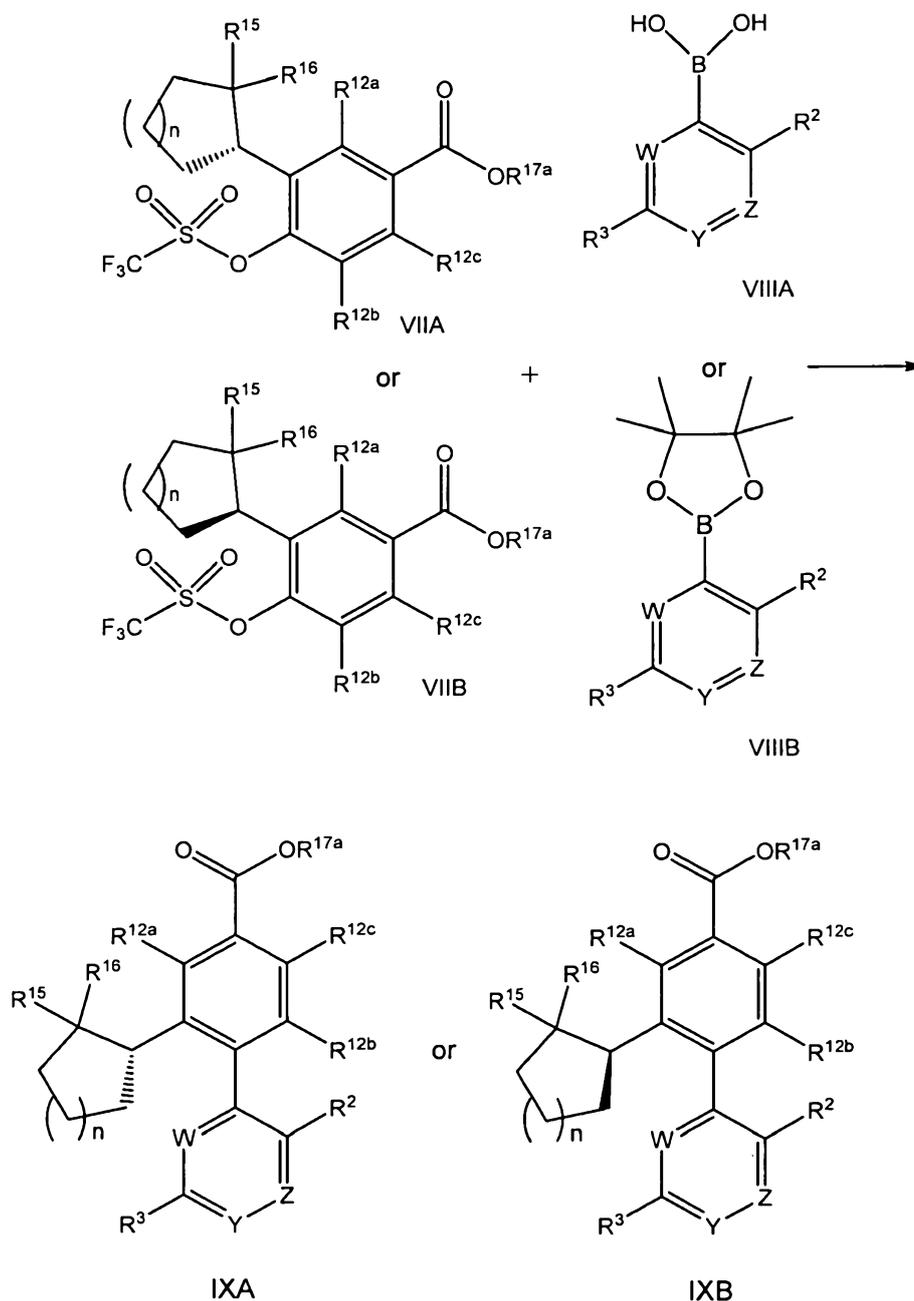
[0216] Compounds of formula **VIA** and **VIB** may be used to synthesize the biphenyl tail groups used to prepare the example compounds of the present invention. Therefore, in some embodiments, where R¹⁴ is -OH (compounds of formula **VIA'** and **VIB'**) compounds of formula **VIA'** and/or **VIB'** are converted to compounds of **VIIA** and/or **VIIB** as shown in Scheme 4 by reacting them with N-phenyl-bis(trifluoromethanesulfonimide) or with trifluoromethanesulfonic anhydride. Typically, this reaction is accomplished in a suitable solvent such as dichloromethane with triethylamine and dimethylaminopyridine. Therefore, in some embodiments, the process further includes reacting a compound of formula **VIA'** and/or **VIB'** with N-phenyl-bis(trifluoromethanesulfonimide) or with trifluoromethanesulfonic anhydride to form a compound of formula **VIIA** or **VIIB** where the variables have any of the values set forth herein.

Scheme 4



[0217] Compounds of formula **VIIA** and **VIIB** are very useful intermediates and can be used to synthesize numerous biphenyl or phenylpyridyl compounds that may be used to construct the compounds of the invention. For example, as shown in Scheme 5, compounds **VIIA** and **VIIB** can be reacted with boronic acids or boronates (**VIIIA** or **VIIIB**) to provide biphenyl compounds **IXA** or **IXB** using the conditions set forth herein. Therefore, in some embodiments, the process further includes reacting a compound of formula **VIIA** and/or **VIIB** with a compound of formula **VIIIA** or **VIIIB** to form a compound of formula **IXA** or **IXB** where the variables have any of the values set forth herein.

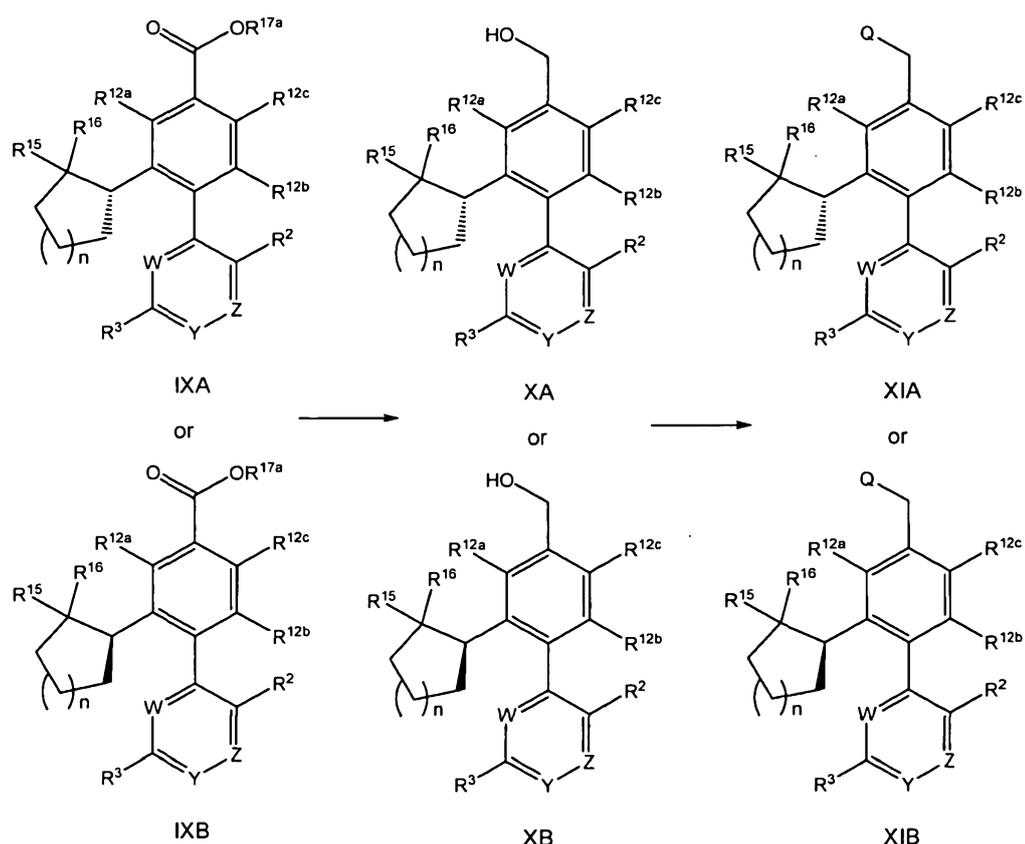
Scheme 5



[0218] Esters of formula **IXA** and **IXB** are also useful intermediates and can be used to synthesize compounds of the invention after reduction to the hydroxymethyl compounds **XA** or **XB** or subsequent conversion to the chloromethyl or bromomethyl compounds **XIA** or **XIB** where $\text{Q} = \text{Cl}$ or Br . For example, as shown in Scheme 6, compounds **IXA** and **IXB** can be reduced with reducing agents such as lithium aluminum hydride using the conditions set forth herein to provide hydroxymethyl compounds **XA** or

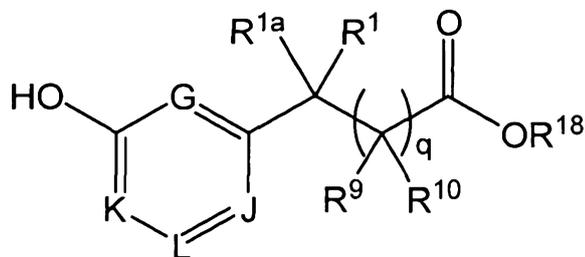
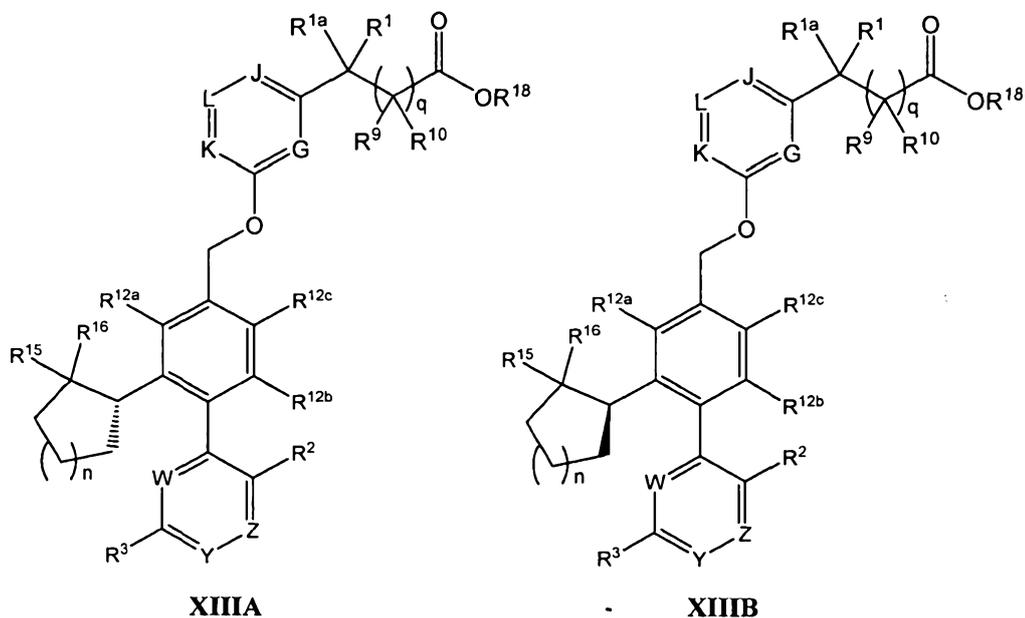
XB which may then be converted to halomethyl compounds with reagents such as thionyl chloride to provide compounds such as **XIA** or **XIB** where the variables have any of the values set forth herein. Therefore, in some embodiments, the method further comprising reducing a compound of formula **IXA** or **IXB** with a reducing agent such as LAH to form a compound of formula **XA** or **XB**. In some such embodiments, the method further comprises converting the hydroxyl functional group of a compound of formula **XA** or **XB** to a chloride or a bromide to form a compound of formula **XIA** or **XIB**.

Scheme 6



[0219] Hydroxymethyl compounds **XA** or **XB** and chloromethyl or bromomethyl compounds **XIA** or **XIB** may be reacted with ester compounds of formula **XII** to form compounds of formula **XIIIA** or **XIIIB** using the reaction conditions set forth herein where R^{18} is a (C_1 - C_6)alkyl group and the other variables have any of the values set forth herein. Therefore, in some embodiments, the method further includes reacting a compound of formula **XA** or **XB** or a compound of formula **XIA** or **XIB** with a compound of formula **XII** to form a compound of formula **XIIIA** or **XIIIB**. Esters **XIIIA** and **XIIIB**, which are compounds of formula **I**, can then be saponified using the

conditions described herein to form compounds of formula **XIVA** and **XIVB** where the variables have any of the values set forth herein. Therefore, some embodiments include saponifying a compound of formula **XIIIA** or **XIIIB** to form a compound of formula **XIVA** or **XIVB** where R^{18} is a (C₁-C₆)alkyl group and the other variables have any of the values set forth herein.

**XII****XIIIA****XIIIB**

carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition, the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases.

[0224] The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with other non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid, or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in U.S. Patent Nos. 4,256,108, 4,160,452, and 4,265,874 to form osmotic therapeutic tablets for control release.

[0225] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate, or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[0226] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for

example polyoxy-ethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0227] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil, or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin, or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0228] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0229] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

[0230] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, and flavoring and coloring agents.

[0231] The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0232] The pharmaceutical compositions may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include, for example, cocoa butter and polyethylene glycols.

[0233] For topical use, creams, ointments, jellies, solutions, or suspensions, etc., containing the compounds of the invention are employed. As used herein, topical application is also meant to include the use of mouthwashes and gargles.

[0234] The pharmaceutical compositions and methods of the invention may further comprise other therapeutically active compounds, as noted herein, useful in the treatment of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema.

6.2.4 Methods of Use

[0235] In another aspect, the invention provides methods of treating a disease or condition selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia,

metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema. The methods comprise administering to a subject in need thereof, a therapeutically effective amount of a compound or composition of any of the embodiments of the invention.

[0236] In one embodiment, the disease or condition is type II diabetes.

[0237] In another aspect, the present invention provides a method for treating a disease or condition responsive to the modulation of GPR40. Such methods comprise administering to a subject in need thereof a therapeutically effective amount of a compound or composition of the invention.

[0238] In some embodiments, the disease or condition is selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema.

[0239] In certain embodiments, the disease or condition is type II diabetes.

[0240] In some embodiments, the disease or condition is obesity.

[0241] In some embodiments, the disease or condition is hypertension.

[0242] In some embodiments of administering the compounds or compositions of the invention, the compound or composition is administered orally, parenterally, or topically. In some embodiments, the compound or composition is administered orally. In other embodiments, the compound or composition is administered parenterally. In other embodiments, the compound or composition is administered topically.

[0243] The compounds of the invention may be administered alone or in combination with one or more other therapeutic agents. Therefore, in some embodiments, the compound or composition of any of the embodiments is administered in combination with a second therapeutic agent. In some such embodiments, the second therapeutic agent is an insulin sensitizing agent, such as metformin or a thiazolidinedione, for example. In some embodiments, the second therapeutic agent is a GLP-1 analog. In some

embodiments, the second therapeutic agent is an inhibitor of DPP-IV such as, but not limited to, sitagliptin.

[0244] In another aspect, the invention provides methods of treating a disease or disorder responsive to modulation of GPR40 comprising administering to a subject having such a disease or disorder, a therapeutically effective amount of one or more of the subject compounds or compositions.

[0245] In yet another aspect, the invention provides methods of treating a GPR40-mediated condition, disease or disorder comprising administering to a subject having such a condition, disease or disorder, a therapeutically effective amount of one or more of the subject compounds or compositions.

[0246] In yet another aspect, the invention provides methods of modulating GPR40 comprising contacting a cell with one or more of the subject compounds or compositions.

[0247] For example, in some embodiments, a cell that constitutively expresses GPR40 is contacted with one or more of the subject compounds or compositions.

[0248] In certain embodiments, a cell to be contacted can be made to express or overexpress GPR40, for example, by expressing GPR40 from heterologous nucleic acid introduced into the cell or, as another example, by upregulating the expression of GPR40 from nucleic acid endogenous to the cell.

[0249] Depending on the disease to be treated and the subject's condition, the compounds of the invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (e.g., transdermal, local) routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. The invention also contemplates administration of the compounds of the invention in a depot formulation, in which the active ingredient is released over a defined time period.

[0250] In the treatment or prevention type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic

retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema or other conditions or disorders associated with GPR40, an appropriate dosage level will generally be about 0.001 to 100 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.01 to about 25 mg/kg per day; more preferably about 0.05 to about 10 mg/kg per day. A suitable dosage level may be about 0.01 to 25 mg/kg per day, about 0.05 to 10 mg/kg per day, or about 0.1 to 5 mg/kg per day. Within this range, the dosage may be 0.005 to 0.05, 0.05 to 0.5 or 0.5 to 5.0 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets containing from 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 3.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

[0251] It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[0252] The compounds of the invention can be combined or used in combination with other agents useful in the treatment, prevention, suppression or amelioration of the diseases or conditions for which compounds of the invention are useful, including type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema. Such other agents, or drugs, may be administered, by a route and in an amount commonly used therefore, simultaneously or sequentially with a compound of the invention. When a compound of the invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the invention is preferred. Accordingly, the pharmaceutical compositions of the invention include those

that also contain one or more other active ingredients or therapeutic agents, in addition to a compound of the invention.

[0253] The compounds of the invention may be used in combination with a second therapeutic agent such as those described herein. Thus, in some embodiments, therapeutic compositions are provided that include a compound of the invention and a second therapeutic agent as a combined preparation for simultaneous, separate or sequential use in the treatment of a subject with a disease or condition mediated by GPR40. In some embodiments, therapeutic compositions are provided that include a compound of the invention and a second therapeutic agent as a combined preparation for simultaneous, separate or sequential use in the prophylactic treatment of a subject at risk for a disease or condition mediated by GPR40. In some such embodiments, the components are provided as a single composition. In other embodiments, the compound and the second therapeutic agent are provided separately as parts of a kit.

[0254] Examples of other therapeutic agents that may be combined with a compound of the invention, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) cholesterol lowering agents such as HMG-CoA reductase inhibitors (e.g., lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and other statins), bile acid sequestrants (e.g., cholestyramine and colestipol), vitamin B₃ (also known as nicotinic acid, or niacin), vitamin B₆ (pyridoxine), vitamin B₁₂ (cyanocobalamin), fibric acid derivatives (e.g., gemfibrozil, clofibrate, fenofibrate and bezafibrate), probucol, nitroglycerin, and inhibitors of cholesterol absorption (e.g., beta-sitosterol and acylCoA-cholesterol acyltransferase (ACAT) inhibitors such as melinamide), HMG-CoA synthase inhibitors, squalene epoxidase inhibitors and squalene synthetase inhibitors; (b) antithrombotic agents, such as thrombolytic agents (e.g., streptokinase, alteplase, anistreplase and reteplase), heparin, hirudin and warfarin derivatives, β -blockers (e.g., atenolol), β -adrenergic agonists (e.g., isoproterenol), ACE inhibitors and vasodilators (e.g., sodium nitroprusside, nicardipine hydrochloride, nitroglycerin and enalaprilat); and (c) anti-diabetic agents such as insulin and insulin mimetics, sulfonylureas (e.g., glyburide, meglitinide), biguanides, e.g., metformin (GLUCOPHAGE[®]), α -glucosidase inhibitors (acarbose), insulin sensitizers, e.g., thiazolidinone compounds, rosiglitazone (AVANDIA[®]), troglitazone (REZULIN[®]), ciglitazone, pioglitazone (ACTOS[®]) and englitazone, DPP-IV inhibitors, e.g., vildagliptin (Galvus[®]), sitagliptin (Januvia[™]), and GLP-I analogs, e.g., exenatide (Byetta[®]). In some embodiments, a compound of the invention may be administered along with a DPP-IV

inhibitor or a GLP-I analog. In some embodiments, a compound of the invention is administered with any of the DPP-IV inhibitors set forth in U.S. Patent Publication No. 2006/0270701 which is hereby incorporated by reference in its entirety and for all purposes as if specifically set forth herein.

[0255] The weight ratio of the compound of the invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Combinations of a compound of the invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

[0256] In another aspect, the present invention provides a method for modulating circulating insulin concentration in a subject, comprising administering a compound or composition of the invention.

[0257] In some embodiments, the insulin concentration is increased after the compound is administered to the subject.

[0258] In other embodiments, the insulin concentration is decreased after the compound is administered to the subject.

[0259] The compounds and compositions described herein may be used to treat a variety of disease states and conditions. Therefore, in some embodiments, a compound of composition of any of the described embodiments is used for treating a disease or condition selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer, and edema. In some such embodiments, the disease or condition is type II diabetes.

[0260] The compounds of the invention may also be used to modulate GPR 40. Therefore, in some embodiments, a compound or composition of any of the embodiments is used for modulating GPR40.

[0261] The compounds of any of the embodiments described herein may be used to prepare medicaments for treating the diseases or conditions described herein such as type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia,

hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and/or edema. In some embodiment, the disease or condition is type II diabetes. The compounds of any of the embodiments may also be used to prepare medicaments for modulating GPR40 in a subject such as in a mammalian subject with type II diabetes.

[0262] The following examples are offered by way of illustration and are not intended to limit the scope of the invention. Those of skill in the art will readily recognize a variety of noncritical parameters that could be modified to yield essentially similar results.

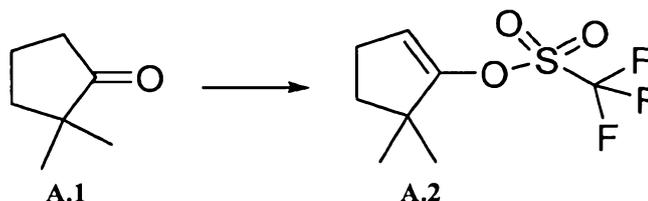
7. EXAMPLES

[0263] Unless otherwise stated, all compounds were obtained from commercial sources or were prepared using the methods and experimental procedures described herein. Various procedures are also set forth in published U.S. Patent Application No. 2006/0004012 which is hereby incorporated by reference in its entirety and for all purposes as if set forth herein. The following abbreviations are used to refer to various reagents, solvents, experimental procedures, or analytical techniques that are described in the examples:

ACN	Acetonitrile
COD	1,5-Cyclooctadiene
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMF	N,N-Dimethylformamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMSO	Dimethylsulfoxide
ESI	Electrospray Ionization
EtOAc	Ethyl acetate
EtOH	Ethanol

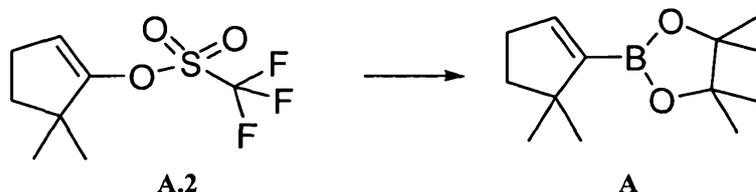
HPLC	High Performance Liquid Chromatography
HSA	Human Serum Albumin
IPA	Isopropanol
LAH	Lithium Aluminum Hydride
LDA	Lithium Diisopropylamide
MeCN	Acetonitrile
MeOH	Methanol
MS	Mass Spectrometry
NBD	Norbornadiene
NMR	Nuclear Magnetic Resonance
-PCy ₂	-P(cyclohexyl) ₂
PPTS	Pyridinium p-Toluenesulfonate
TEA	Triethylamine
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy free radical
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
SPA	Scintillation Proximity Assay

7.1 Intermediate A



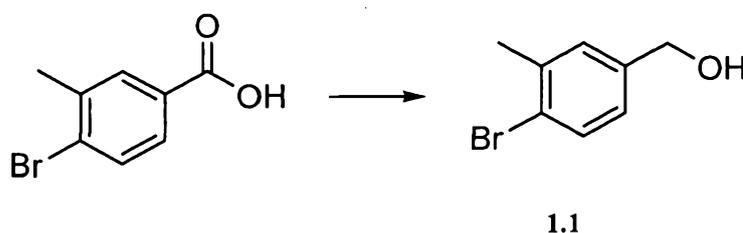
[0264] 5,5-Dimethylcyclopent-1-enyl trifluoromethanesulfonate (A.2). To a solution of 2,2-dimethylcyclopentanone **A.1** (available from ChemSampCo)(3.00 g, 26.75 mmol) in THF (100 mL), was slowly added LDA (14.7 mL, 2.0 M, in heptane) at -78 °C. The resulting mixture was stirred at -78 °C for 1 hour. A solution of N-phenyltriflimide (10.00 g, 28.00 mmol) was added to the mixture at -78 °C, and stirring was continued at 0 °C for 2 hours and then at room temperature overnight. The reaction mixture was extracted with hexane (80× 2 mL). The organic layer was washed with saturated Na₂CO₃ (30 mL), brine (20 mL), and dried with MgSO₄. The solvent was removed, and the crude product was purified by CombiFlash (eluant was EtOAc and hexane) to give **A.2**. ¹H

NMR (CDCl₃) δ ppm 1.16 (s, 6 H), 1.86 (t, J = 7.1 Hz, 2 H), 2.36 (t, J = 7.1 Hz, 2 H), 5.56 (m, 1 H).

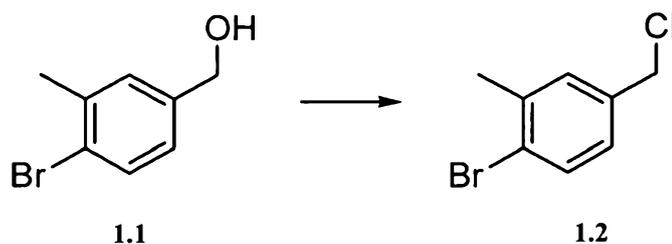


[0265] **2-(5,5-Dimethylcyclopent-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (A).** PdCl₂(PPh₃)₂ (0.56 g, 0.80 mmol), PPh₃ (0.63 g, 2.40 mmol), bis(pinacolato)diboron (6.80 g, 26.75 mmol) and KOPh (fine powder, 5.30 g, 40.10 mmol) were added to a flask. The flask was flushed with nitrogen and charged with toluene (100 mL) and with A.2 (6.53 g, 26.75 mmol). The mixture was stirred at 50 °C for 2 hours. The reaction mixture was treated with water at room temperature and extracted with benzene (60 × 2 mL). The organic layer was dried over MgSO₄. The product was then purified by CombiFlash to give Intermediate A. ¹H NMR (CDCl₃) δ ppm 1.04 (s, 6 H), 1.18 (s, 12 H), 1.57 (t, J = 7.1 Hz, 2 H), 2.29 (t, J = 7.1 Hz, 2 H), 6.29 (m, 1 H).

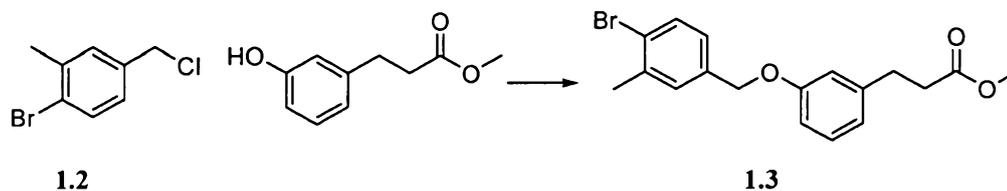
[0266] **Example 1**



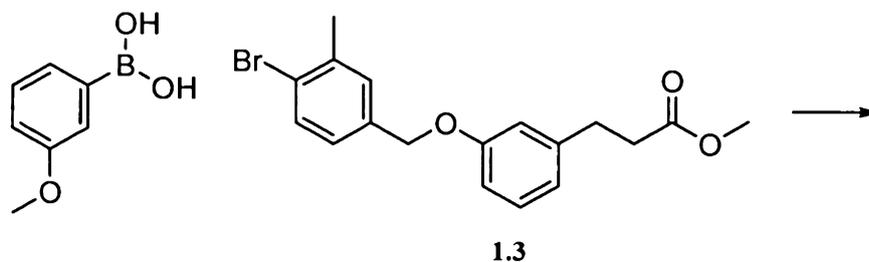
[0267] **(4-Bromo-3-methylphenyl)methanol (1.1).** A solution of 4-bromo-3-methylbenzoic acid (available from Aldrich) (4.0 g, 18.6 mmol) in THF (20 mL) was treated with borane THF complex (27.9 mL, 27.9 mmol) and allowed to stir overnight at room temperature. The reaction mixture was quenched with MeOH, diluted with EtOAc, washed with water, brine, the organics dried over Na₂SO₄ and concentrated. The crude was purified by combiflash (0 to 40% EtOAc/ hexane) yielding 1.1 (3.09 g, 82.6% yield).

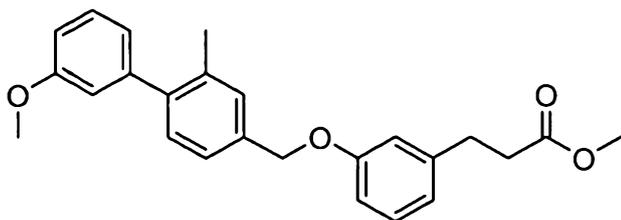


[0268] 1-Bromo-4-(chloromethyl)-2-methylbenzene (1.2). To a stirred solution of **1.1** (2.0 g, 9.947 mmol) in DCM (50 mL) at 23 °C was added thionyl chloride (1.451 mL, 19.89 mmol) and allowed to stir overnight. The reaction was concentrated and then purified by combiflash (0 to 10% EtOAc/ hexanes) to provide **1.2** (1.9940 g, 91.32% yield).



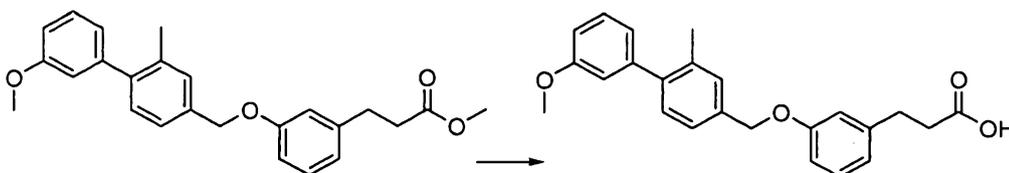
[0269] Methyl 3-(3-(((4-bromo-3-methylphenyl)methyl)oxy)phenyl)propanoate (1.3). To flask containing methyl 3-(3-hydroxyphenyl)propanoate (available from Aagile Labs Division of Tyger Scientific) (0.25g, 1.387 mmol) and cesium carbonate (0.5876 g, 1.804 mmol) in DMF (8 mL), was added **1.2** (0.3654 g, 1.665 mmol). The resulting mixture was then stirred overnight. The reaction was diluted with water and extracted with EtOAc. The organic layers were washed with brine, dried over Na₂SO₄, filtered, concentrated, and then purified by combiflash (0 to 20% EtOAc/ hexane) to provide **1.3** (0.4575 g, 90.78% yield). MS ESI (pos.) m/e: 382.0 (M+H₂O)⁺.





1.4

[0270] **Methyl 3-(3-(((2-methyl-3'-(methoxy)-1,1'-biphenyl-4-yl)methoxy)phenyl)propanoate (1.4).** To a 2 dram vial charged with methyl ester **1.3** (0.0700 g, 0.193 mmol), tetrakis(triphenylphosphine)palladium (0) (0.0445 g, 0.0385 mmol), cesium fluoride (0.0356 mL, 0.964 mmol), and 3-methoxyphenylboronic acid (available from Aldrich)(0.0878 g, 0.578 mmol), was added DME (1 mL). The resulting mixture was then heated at 85 °C overnight. The reaction was allowed to cool and then filtered and concentrated. The crude product was purified by combiflash (0 to 20% EtOAc/ hexanes) yielding **1.4** (0.0624 g, 82.9% yield). MS ESI (pos.) m/e: 391.1 (M+H)⁺.

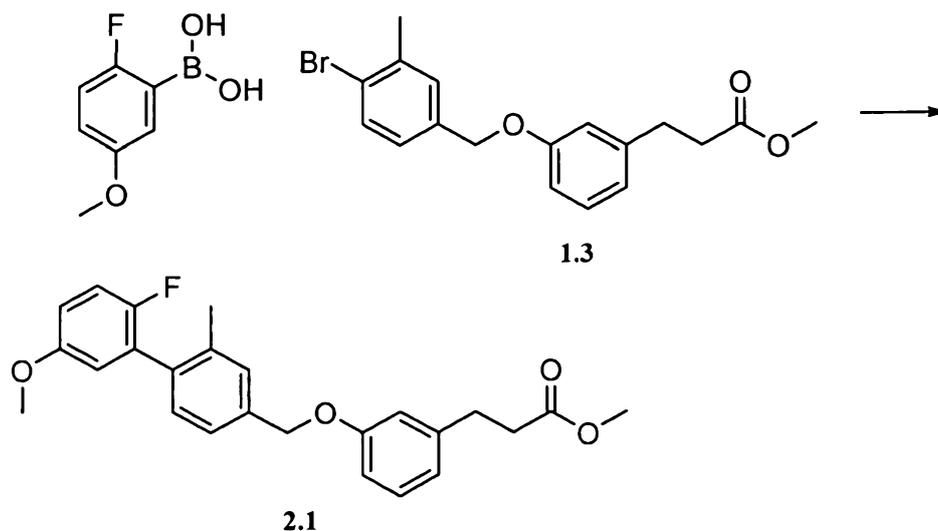


1.4

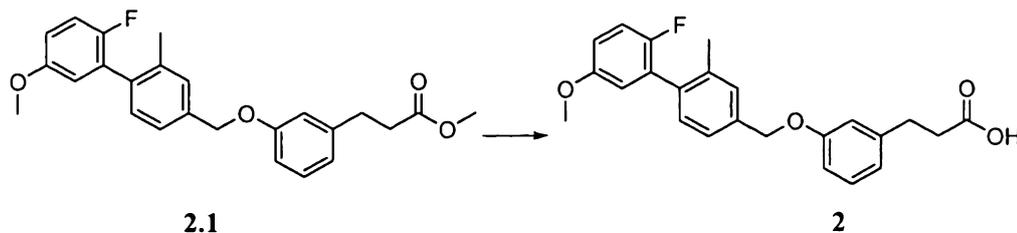
1

[0271] **3-(3-(((2-Methyl-3'-(methoxy)-1,1'-biphenyl-4-yl)methoxy)phenyl)propanoic acid (1).** To a solution of **1.4** (0.0532 g, 0.136 mmol) in THF/MeOH (2/1) (1.5 mL) was added LiOH (0.50 mL, 0.500 mmol). The resulting mixture was stirred overnight at 23 °C, quenched with excess 1N HCl, and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The crude residue was purified by combiflash (0 to 40% EtOAc/hexane) to afford **1** (0.0426 g, 83.1% yield). MS ESI (neg.) m/e: 375.1 (M-H)⁻. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.32 - 7.39 (3 H, m), 7.24 - 7.31 (2 H, m), 6.85 - 6.95 (6 H, m), 5.08 (2 H, s), 3.87 (3 H, s), 2.99 (2 H, t, J=7.8 Hz), 2.73 (2 H, t, J=7.8 Hz), 2.34 (3 H, s).

[0272] **Example 2**

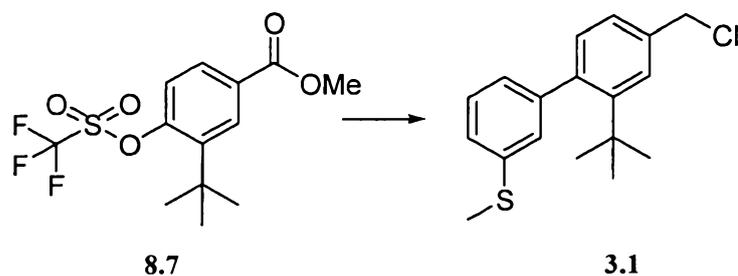


[0273] **Methyl 3-(3-(((2-methyl-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (2.1).** Compound **1.3** (0.070 g, 0.193 mmol) was coupled with 2-fluoro-5-methoxyphenylboronic acid (available from Aldrich)(0.0982 g, 0.578 mmol) according to the method reported for preparation of **1.4** to afford **2.1** (0.070 g, 89%) as a colorless oil.

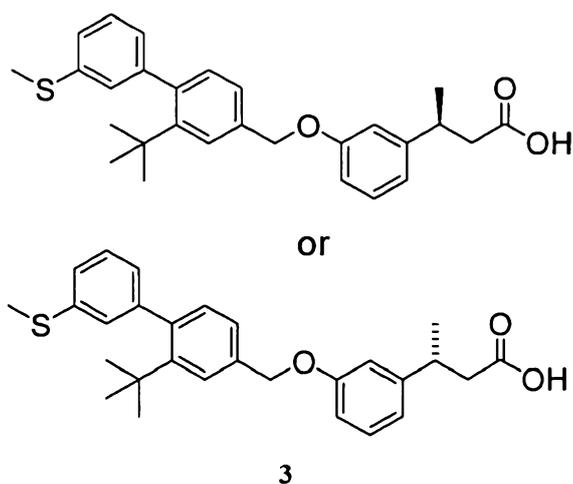
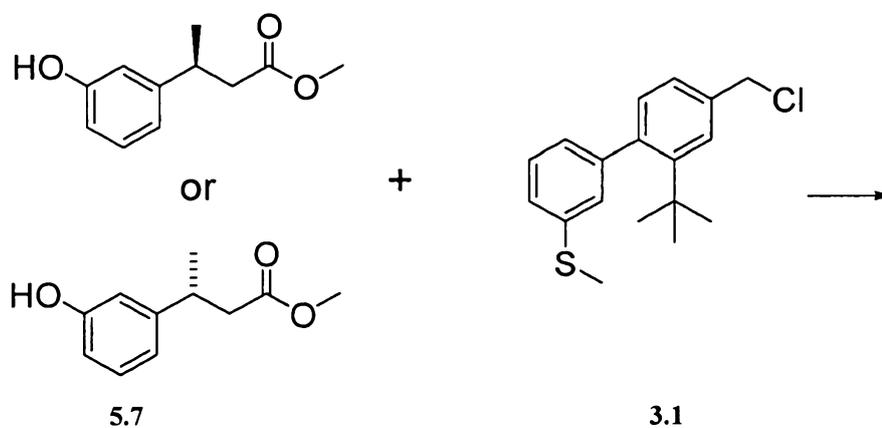


[0274] **3-(3-(((2'-Fluoro-2-methyl-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (2).** To a solution of **2.1** (0.0560 g, 0.137 mmol) in THF/MeOH (2/1) (1.5 mL) was added LiOH (0.50 mL, 0.500 mmol). The resulting mixture was stirred overnight at 23 °C, quenched with excess 1N HCl, and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The crude residue was purified by combiflash (0 to 40% EtOAc/hexanes) to afford **2** (0.0395 g, 73.0% yield). MS ESI (neg.) m/e: 393.1 (M-H)⁻. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.32 - 7.41 (2 H, m), 7.24 - 7.29 (2 H, m), 7.08 (1 H, t, J=9.0 Hz), 6.85 - 6.92 (4 H, m), 6.79 (1 H, dd, J=5.9, 3.1 Hz), 5.08 (2 H, s), 3.83 (3 H, s), 2.98 (2 H, t, J=7.8 Hz), 2.72 (2 H, t, J=7.6 Hz), 2.27 (3 H, s).

[0275] **Example 3**

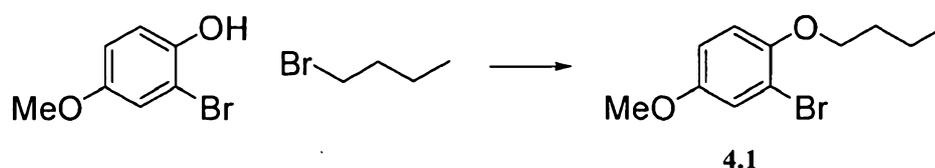


[0276] **4-(Chloromethyl)-2-(1,1-dimethylethyl)-3'-(methylsulfanyl)-1,1'-biphenyl (3.1)**. The title compound was synthesized in a similar manner as **12.3** starting from **8.7** and 3-thiomethylphenylboronic acid (available from Aldrich). ^1H NMR (500 MHz, CDCl_3) δ ppm 7.54 (1 H, d, $J=2.0$ Hz), 7.28 (4H, m), 7.15 (1H, t, $J=1.7$ Hz), 7.05 (2H, m), 4.65 (2 H, s), 2.49 (3H, s), 1.22 (9H, s).

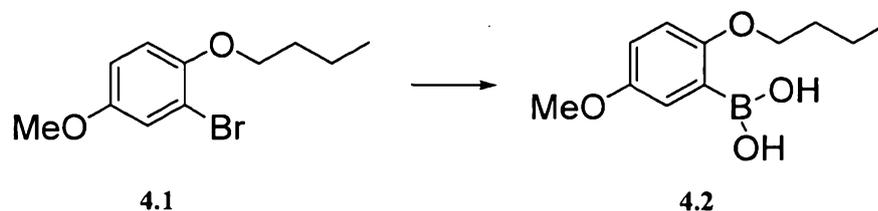


[0277] (3R)-3-(3-(((2-(1,1-Dimethylethyl)-3'-(methylsulfonyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-3'-(methylsulfonyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (3). Compound 3 was prepared from 5.7 and 3.1 using the coupling and hydrolysis techniques for preparing compounds reported in US 2006/0004012. (MS ESI (neg.) m/e: 447.1 (M-H). ¹H NMR (500 MHz) (CDCl₃) δ ppm 7.62 (1 H, d, J=1.2 Hz), 7.32 (4 H, m), 7.20 (1 H, s), 7.10 (2 H, m), 6.95 (2 H, m), 6.89 (1 H, d, J=7.6 Hz), 5.11 (2 H, s), 3.35 (1 H, m), 2.76 (1 H, m), 2.65 (1 H, m), 2.51 (3 H, s), 1.36 (3 H, d, J=7.1 Hz), 1.25 (9 H, s).

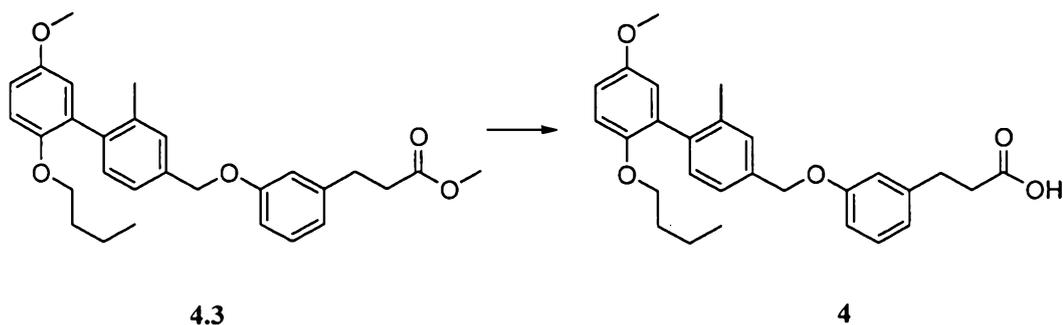
[0278] **Example 4**



[0279] **2-Bromo-1-butoxy-4-methoxybenzene (4.1)**. A mixture of 2-bromo-4-methoxyphenol (available from Betapharma Inc.)(1.50 g, 7.39 mmol), 1-bromobutane (available from Aldrich)(0.95 mL, 8.87 mmol), and cesium carbonate (3.13 g, 9.60 mmol) in DMF (40 mL) was stirred overnight at room temperature. The mixture was diluted with EtOAc, washed with water and brine, dried over Na₂SO₄, and concentrated. The crude product was purified by silica gel flash chromatography (0-20% EtOAc/hexane) to afford compound 4.1 (1.49 g, 78% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.15 (d, J=2.7 Hz, 1H), 6.84 (d, J=9.0 Hz, 1H), 6.80 (dd, J=3.1, 9.0 Hz, 1H), 3.97 (t, J=6.5 Hz, 2H), 3.76 (s, 3H), 1.79 (m, 2H), 1.53 (m, 2H), 0.98 (t, J=7.2 Hz, 3H).

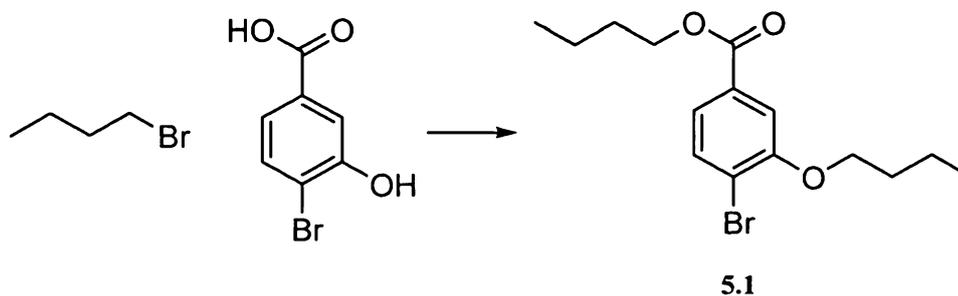


[0280] **2-Butoxy-5-methoxyphenylboronic acid (4.2)**. To a -78 °C solution of 2-bromo-1-butoxy-4-methoxybenzene 4.1 (250 mg, 965 μmol) in THF (8.0 mL) was added tert-butyllithium, 1.7 M solution in pentane (1248 μL, 2122 μmol) dropwise under a blanket of nitrogen. The pale yellow solution was stirred for 0.5 h at -78°C before dropwise addition of neat trimethyl borate (175 μL, 1544 μmol) at the same temperature. The resulting mixture was stirred for 1 hour at -78°C, warmed to 25°C, and stirred for an

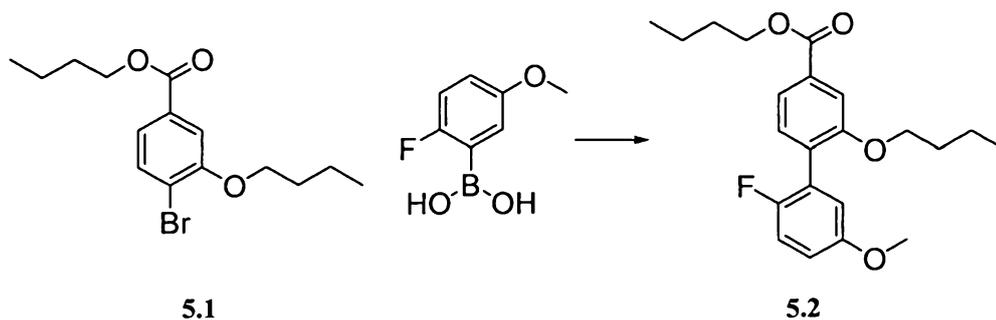


[0282] **3-(3-(((2'-(Butyloxy)-2-methyl-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (4).** To a solution of **4.3** (0.0241 g, 0.0521 mmol) in THF/MeOH (2/1) (1.5 mL) was added LiOH (0.50 mL, 0.500 mmol). The resulting mixture was stirred overnight at 23°C, quenched with excess 1N HCl, and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The crude residue was purified by combiflash (0 to 40% EtOAc/hexanes) to afford **4** (0.0166 g, 71.0% yield). MS ESI (neg.) m/e: 393.1 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.32 (1 H, s), 7.20 - 7.29 (4 H, m), 6.83 - 6.92 (5 H, m), 6.74 (1 H, d, J=2.9 Hz), 5.07 (2 H, s), 3.83 (2 H, t, J=6.6 Hz), 3.79 (3 H, s), 2.97 (2 H, t, J=7.8 Hz), 2.68 - 2.73 (2 H, m), 2.19 (3 H, s), 1.53 - 1.60 (2 H, m), 1.22 - 1.31 (2 H, m), 0.83 (3 H, t, J=7.3 Hz).

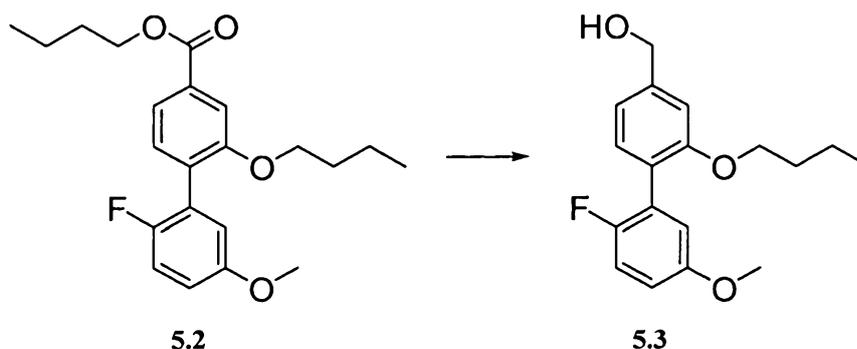
[0283] **Example 5**



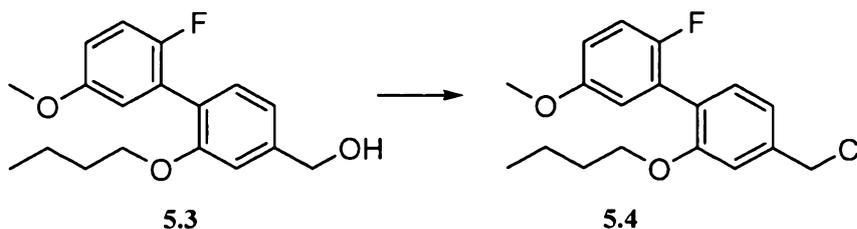
Butyl 4-bromo-3-(butyloxy)benzoate (5.1). To a flask containing 4-bromo-3-hydroxybenzoic acid (available from Combi-Blocks Inc.)(2.40 g, 11.06 mmol) and cesium carbonate (8.287 g, 25.44 mmol) in DMF (40 mL), was added 1-bromobutane (available from Aldrich)(2.494 mL, 23.22 mmol), and the mixture was stirred overnight. The reaction was diluted with water and extracted with EtOAc. The organic layers were washed with brine, dried over Na₂SO₄, filtered, concentrated, and then purified by combiflash (0 to 20% EtOAc/ Hexanes) to provide **5.1** (2.4326 g, 66.81% yield).



[0284] Butyl 2-(butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (5.2). To a 2 dram vial charged with 2-fluoro-5-methoxyphenylboronic acid (available from Aldrich)(2.323 g, 13.67 mmol), tetrakis(triphenylphosphine) palladium(0) (0.7897 g, 0.6834 mmol), cesium fluoride (0.8409 mL, 22.78 mmol), and 5.1 (1.50 g, 4.556 mmol), was added DME (20 mL), and the mixture was then heated at 90 °C overnight. The reaction was allowed to cool and then filtered and concentrated. The crude product was purified by combiflash (0 to 10% EtOAc/ hexanes) yielding 5.2 (1.1530 g, 67.58% yield).

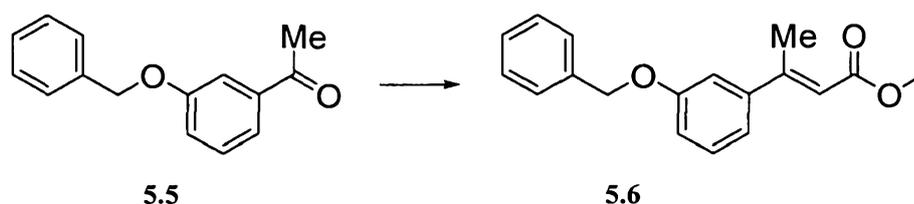


[0285] (2-(Butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (5.3). To 5.2 (1.1530 g, 3.079 mmol) in THF (10 mL) at 0 °C was added LAH (1.0 M solution in THF (4.619 mL, 4.619 mmol)). The reaction was stirred for one hour and then carefully diluted with water, extracted with EtOAc, washed with brine, dried over sodium sulfate, filtered, and concentrated to provide 5.3 (0.9050 g, 96.57% yield).

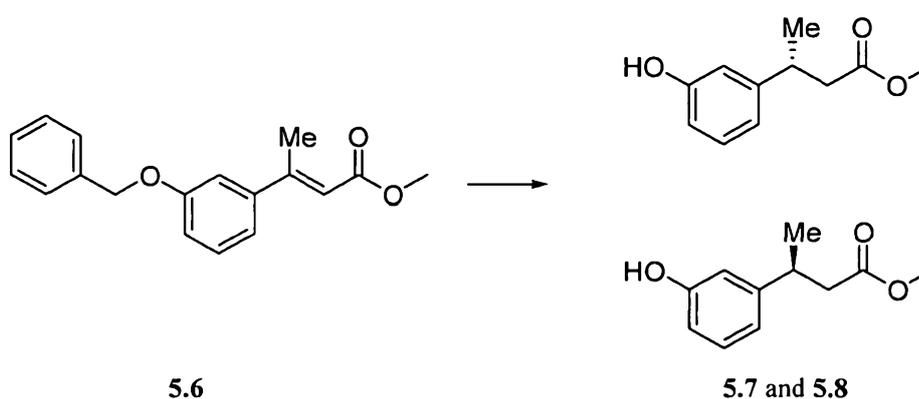


2-(Butyloxy)-4-(chloromethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl

(5.4). To a stirred solution of 5.3 (0.8800 g, 2.891 mmol) in DCM (15 mL) at 23 °C was added thionyl chloride (0.4218 mL, 5.783 mmol). The reaction mixture was then stirred overnight. The reaction was concentrated and then purified by combiflash (0 to 10% EtOAc/ Hexanes) to provide 5.4 (0.7980 g, 85.50% yield).

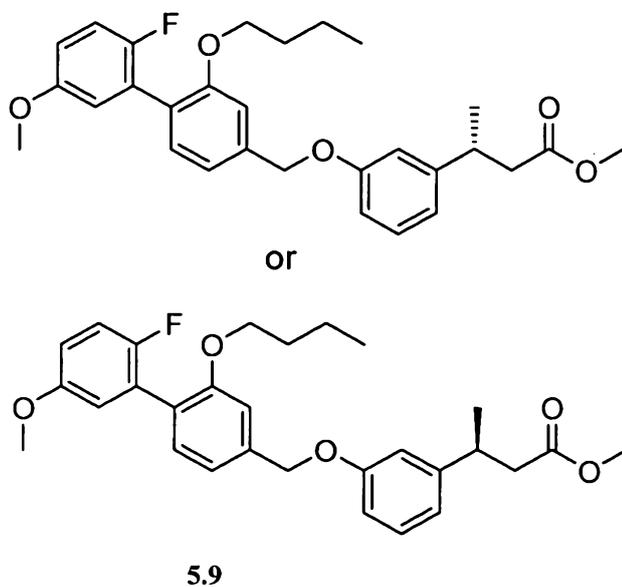
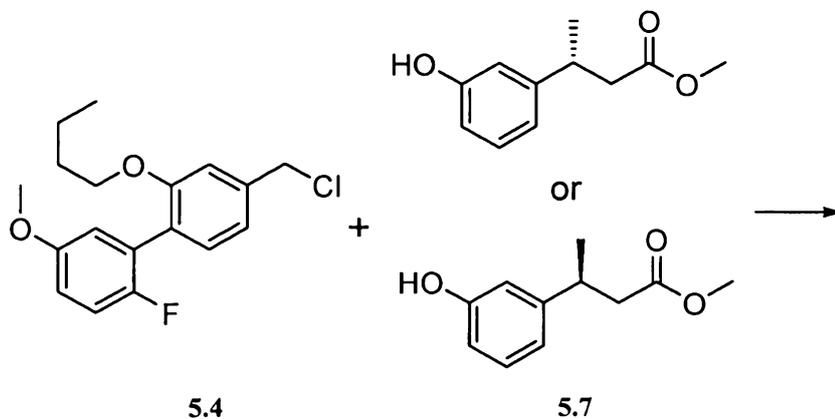


[0286] **Methyl (2E)-3-(3-((benzyl)oxy)phenyl)-2-butenoate (5.6).** To a suspension of lithium chloride (0.28 g, 6.6 mmol) in MeCN (9 mL) were added trimethyl phosphonoacetate (0.76 mL, 5.3 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.79 mL, 5.3 mmol), and 3-benzyloxyacetophenone (available from Aldrich)(1.00 g, 4.4 mmol). The mixture was stirred overnight at reflux (100 °C), cooled to room temperature, diluted with EtOAc, washed with water and brine, dried (MgSO₄), and concentrated. The crude product was chromatographed on silica gel (0-10% EtOAc/hexane) to afford 5.6 (0.45 g, 36%) as a colorless oil.

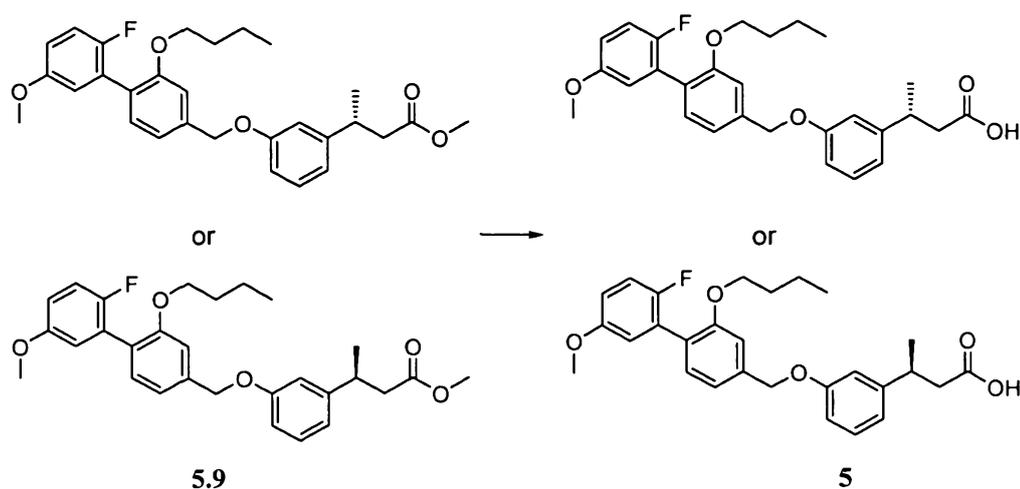


[0287] **Methyl (3R)-3-(3-hydroxyphenyl)butanoate and methyl (3S)-3-(3-hydroxyphenyl)butanoate (5.7 and 5.8).** To a solution of 5.6 (0.44 g, 1.56 mmol) in 1:1 EtOAc/MeOH (10.0 mL), was added 10% Pd/C (0.25 g, 0.23 mmol) under a blanket of N₂. The mixture was sparged with H₂, stirred overnight under a H₂ balloon, filtered through silica gel (EtOAc), and concentrated. The resulting racemate was resolved by

chiral HPLC (Chiralcel OD column, 3% IPA/hexane, 220 nm) to afford **5.7** (0.14 g, 22.7 minutes) and **5.8** (0.14 g, 36.1 minutes) as pale yellow oils.

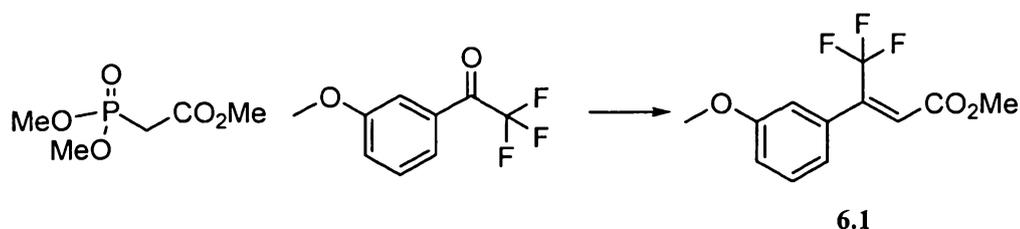


[0288] Methyl (3R)-3-(3-(((2-(butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate or methyl (3S)-3-(3-(((2-(butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate (**5.9**). To flask containing **5.7** (0.0250 g, 0.129 mmol) and cesium carbonate (0.0545 g, 0.167 mmol) in DMF (1 mL) was added **5.4** (0.0499 g, 0.154 mmol). The resulting mixture was then stirred overnight. The reaction was diluted with water and extracted with EtOAc. The organic layers were washed with brine, dried over Na₂SO₄, filtered, concentrated, and then purified by combiflash (0 to 20% EtOAc/ Hexanes) to provide **5.9**.



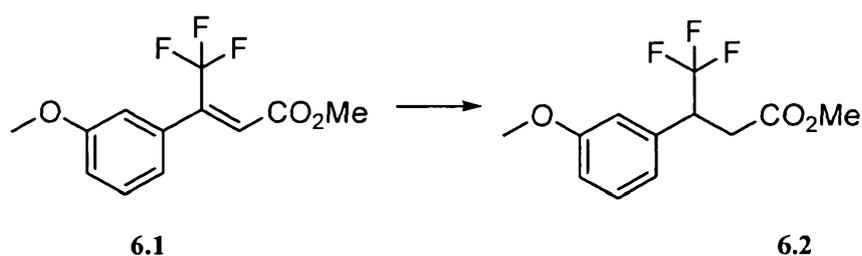
[0289] (3R)-3-(3-(((2-(Butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (**5**). To a solution of **5.9** (0.0620 g, 0.129 mmol) in THF/MeOH (2/1) (1.5 mL), was added lithium hydroxide (0.500 mL, 0.500 mmol). The resulting mixture was stirred overnight at 23 °C, quenched with excess 1N HCl, and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The crude residue was purified by combiflash (0 to 40% EtOAc/hexanes) to afford **5** (0.0519 g, 86.2% yield). MS ESI (neg.) m/e: 465.2 (M-H)⁺. ¹H NMR (500 MHz, CDCl₃) δ ppm 7.25 - 7.32 (2 H, m), 7.02 - 7.10 (3 H, m), 6.83 - 6.92 (5 H, m), 5.09 (2 H, s), 4.01 (2 H, t, J=6.5 Hz), 3.81 (3 H, s), 3.25 - 3.32 (1 H, m), 2.68 - 2.73 (1 H, m), 2.57 - 2.63 (1 H, m), 1.66 - 1.72 (2 H, m), 1.33 - 1.42 (5 H, m), 0.91 (3 H, t, J=7.5 Hz).

[0290] Example 6

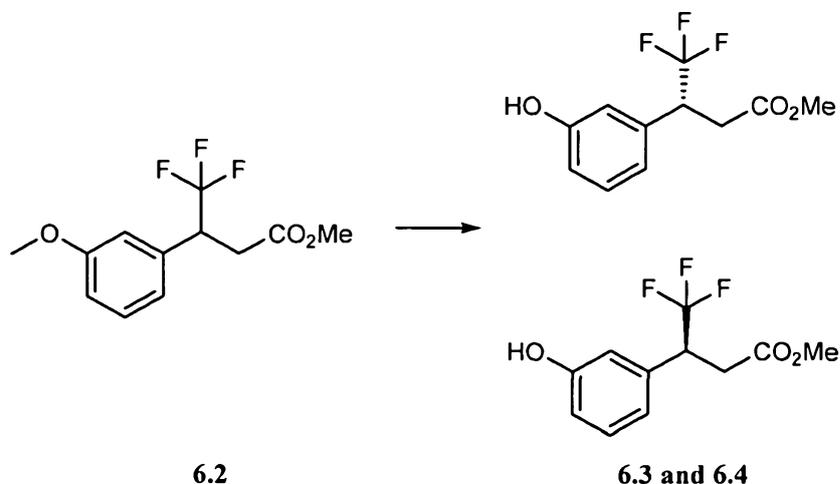


[0291] Methyl (2Z)-4,4,4-trifluoro-3-(3-(methoxy)phenyl)-2-buten-1-yl ester (**6.1**). To a suspension of lithium chloride (0.623 g, 14.7 mmol) in MeCN (20 mL), were added trimethylphosphonoacetate (available from Aldrich)(1.70 mL, 11.8 mmol), DBU (1.76 mL, 11.8 mmol), and 2,2,2-trifluoro-1-(3-methoxyphenyl)ethanone (available from

Oakwood Products Inc.) (2.0 g, 9.80 mmol) at room temperature. The pale yellow mixture was heated to reflux and stirred overnight. The mixture was partitioned between water and EtOAc. The layers were separated, and the aqueous phase was extracted with additional EtOAc. The combined organic layers were washed with 1 N HCl and brine, dried over Na₂SO₄, and concentrated. The crude product was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to afford **6.1** (2.49 g, 97.7% yield) as a colorless oil.

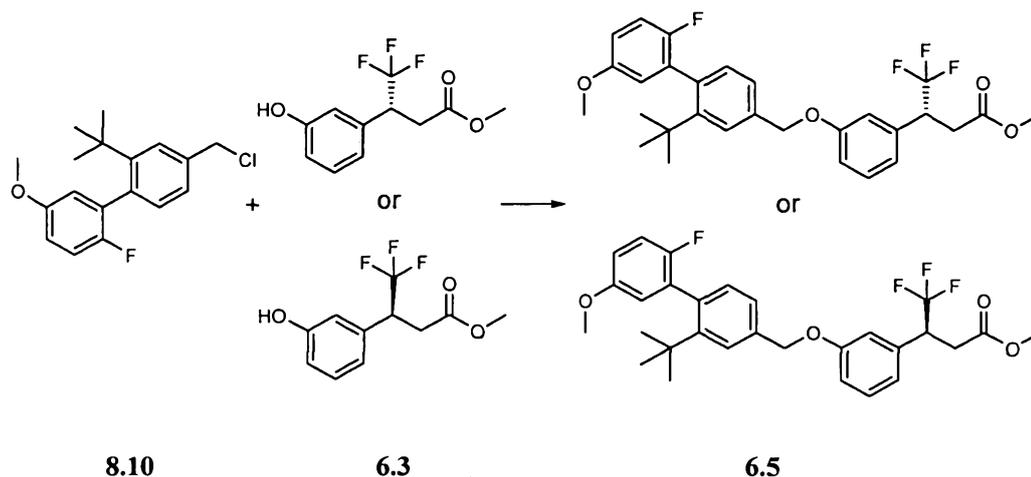


[0292] **Methyl 4,4,4-trifluoro-3-(3-(methoxy)phenyl)butanoate (6.2).** A 250 mL flask containing a solution of **6.1** (2.20 g, 8.5 mmol) in 1:1 EtOAc/MeOH (40 mL) was purged with N₂. To the mixture was added palladium, 10 wt. % (dry), on carbon powder, wet (0.90 g, 0.85 mmol). The vial was then purged with H₂, and the contents were stirred overnight under a H₂ balloon. The black mixture was filtered through a pad of Celite and concentrated to afford **6.2** (2.19 g, 99% yield).

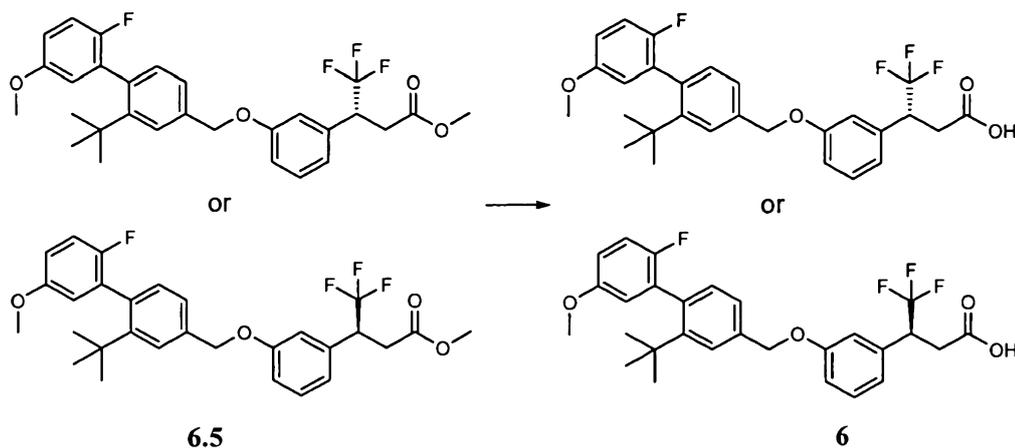


[0293] **Methyl (3R)-4,4,4-trifluoro-3-(3-hydroxyphenyl)butanoate and methyl (3S)-4,4,4-trifluoro-3-(3-hydroxyphenyl)butanoate (6.3 and 6.4).** To a solution of methyl ether **6.2** (1.9546 g, 7.45 mmol) in DCE (60 mL), was added 1,2-

ethanedithiol (9.99 mL, 119 mmol) followed by anhydrous aluminum chloride (7.95 g, 59.6 mmol) at 0 °C. The reaction mixture was allowed to slowly warm to room temperature over four hours and then was quenched with saturated Rochelle's salt solution. The mixture was extracted (2 x 50 mL) with DCM. The combined organic layers were washed with water (1 x 40 mL) and brine (1 x 40 mL) and dried over magnesium sulfate. The filtrate was concentrated, and the residue was purified by chromatography (silica, 0 to 30% EtOAc: hexanes) and then the enantiomers were resolved by chiral HPLC (Chiralcel OD-H column, 3% IPA/hexane, 220 nm) to afford **6.3** (28 minutes) and **6.4** (45 minutes).

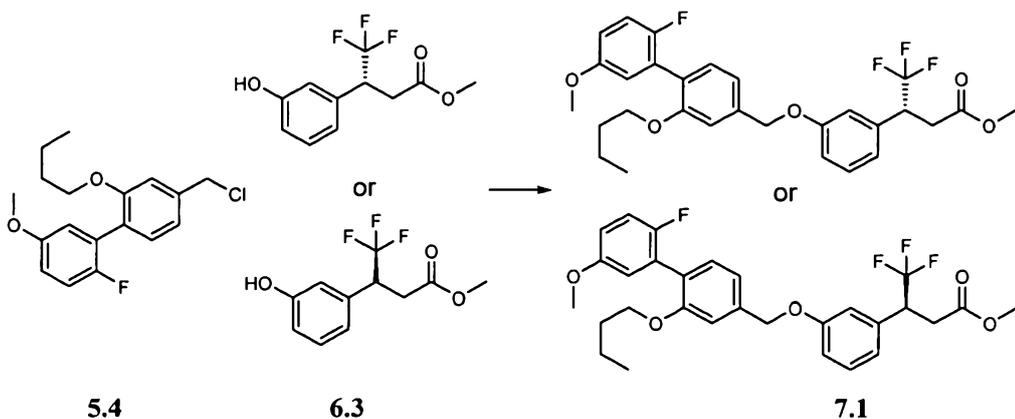


[0294] Methyl (3R)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4,4,4-trifluorobutanoate or methyl (3S)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4,4,4-trifluorobutanoate (**6.5**). To flask containing **6.3** (0.0300 g, 0.121 mmol) and cesium carbonate (0.0512 g, 0.157 mmol) in DMF (1 mL), was added **8.10** (0.0445 g, 0.145 mmol). The resulting mixture was stirred overnight. The reaction was diluted with water and extracted with EtOAc. The organic layers were washed with brine, dried over Na₂SO₄, filtered, concentrated, and then purified by combiflash (0 to 20% EtOAc/ Hexanes) to provide **6.5**.

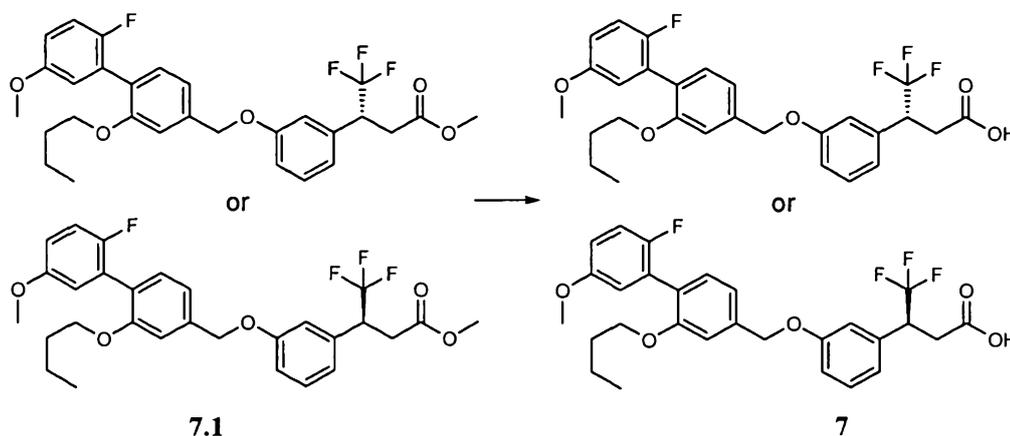


[0295] **(3R)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4,4,4-trifluorobutanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4,4,4-trifluorobutanoic acid (6).** To a solution of **6.4** (0.0627 g, 0.121 mmol) in THF/MeOH (2/1) (1.5 mL), was added lithium hydroxide (0.50 mL, 0.500 mmol). The resulting mixture was stirred overnight at 23 °C, quenched with excess 1N HCl, and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The crude residue was purified by combiflash (0 to 40% EtOAc/hexanes) to afford **6** (0.0449 g, 73.6% yield). MS ESI (neg.) m/e: 503.2 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.61 (1 H, d, J=1.6 Hz), 7.28 - 7.34 (2 H, m), 7.07 (1 H, d, J=7.4 Hz), 6.94 - 7.04 (4 H, m), 6.87 (1 H, dd, J=7.6, 4.5 Hz), 6.79 (1 H, dd, J=5.9, 3.1 Hz), 5.09 (2 H, s), 3.87 (1 H, s), 3.80 (3 H, s), 3.06 (1 H, dd, J=5.1, 16.8 Hz), 2.96 (1 H, dd, J=9.4, 16.8 Hz), 1.25 (9 H, s).

[0296] **Example 7**

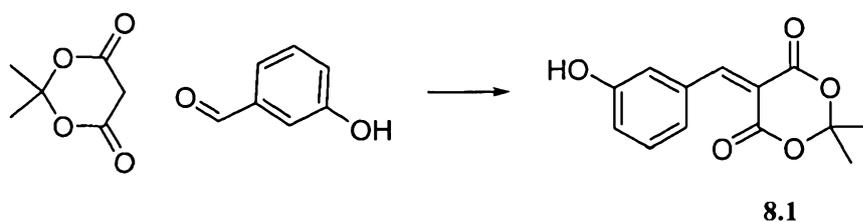


[0297] **Methyl (3R)-3-(3-(((2-(butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4,4,4-trifluorobutanoate or methyl (3S)-3-(3-(((2-(butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4,4,4-trifluorobutanoate (7.1).** To a flask containing **6.3** (0.0300 g, 0.121 mmol) and cesium carbonate (0.0512 g, 0.157 mmol) in DMF (1 mL), was added **5.4** (0.0468 g, 0.145 mmol). The resulting mixture was stirred overnight. The reaction was diluted with water and extracted with EtOAc. The organic layers were washed with brine, dried over Na₂SO₄, filtered, concentrated, and then purified by combiflash (0 to 20% EtOAc/hexanes) to provide **7.1**.

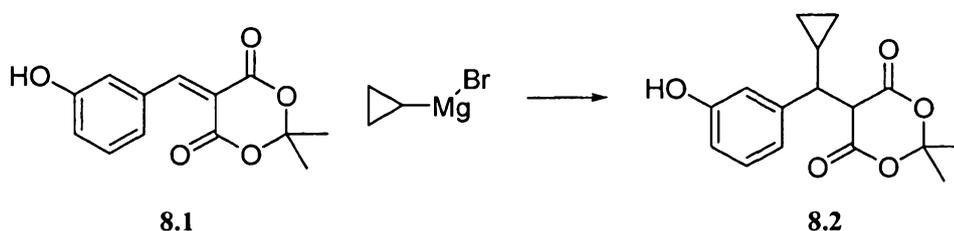


[0298] **(3R)-3-(3-(((2-(Butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4,4,4-trifluorobutanoic acid or (3S)-3-(3-(((2-(butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4,4,4-trifluorobutanoic acid (7).** To a solution of **7.1** (0.0647 g, 0.121 mmol) in THF/MeOH (2/1) (1.5 mL), was added lithium hydroxide (0.500 mL, 0.500 mmol). The resulting mixture was stirred overnight at 23 °C, quenched with excess 1N HCl, and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The crude residue was purified by combiflash (0 to 40% EtOAc/hexanes) to afford **7**. MS ESI (neg.) m/e: 519.2 (M-H)⁻. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.28 - 7.33 (2 H, m), 7.04 - 7.09 (3 H, m), 6.93 - 7.02 (3 H, m), 6.83 - 6.91 (2 H, m), 5.08 (2 H, s), 4.00 (2 H, t, J=6.5 Hz), 3.88 (1 H, td, J=9.2, 4.7 Hz), 3.81 (3 H, s), 3.04 - 3.11 (1 H, m), 2.90 - 2.98 (1 H, m), 1.64 - 1.72 (2 H, m), 1.34 - 1.44 (2 H, m), 0.90 (3 H, t, J=7.2 Hz).

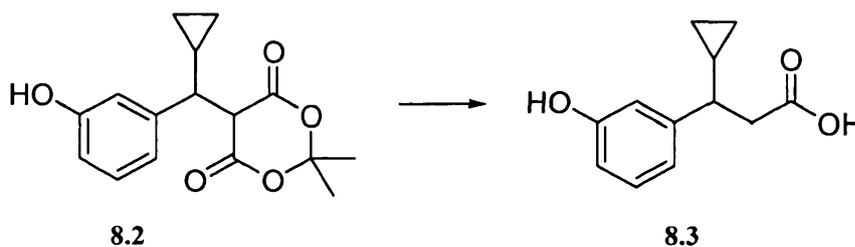
[0299] **Example 8**



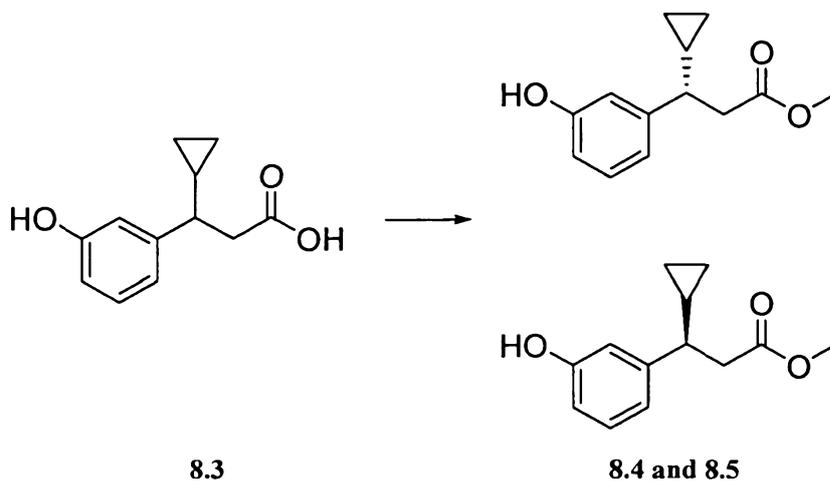
[0300] **5-((3-Hydroxyphenyl)methylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (8.1).** To 3-hydroxybenzaldehyde (available from Aldrich)(24.4 g, 200 mmol) in water (1000 mL) at 85 °C, was added 2,2-dimethyl-1,3-dioxane-4,6-dione (available from Aldrich)(28.8 g, 200 mmol). The resulting mixture was then stirred at 85 °C for 2 hours. The reaction was allowed to cool and then filtered to provide **8.1** (41.3508 g, 83.3% yield) as a yellow solid.



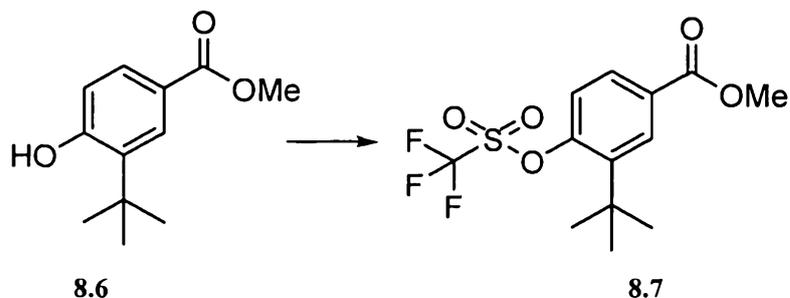
[0301] **5-(Cyclopropyl(3-hydroxyphenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (8.2).** To a solution of **8.1** (2.0 g, 8.06 mmol) in THF, was added cyclopropylmagnesium bromide (available from Aldrich)(96.7 mL, 48.3 mmol) via cannula at 0 °C. The resulting heterogeneous mixture was warmed to room temperature, stirred for 30 minutes, and quenched with 1 N aq. HCl. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried sodium sulfate, filtered, and concentrated. The crude product was purified by silica gel flash chromatography (10-35% EtOAc/hexane) to afford **8.2** (2.04 g, 87.2% yield) as a yellow oil.



[0302] **3-Cyclopropyl-3-(3-hydroxyphenyl)propanoic acid (8.3).** Compound **8.2** (1.71 g, 5.89 mmol) in DMF/water (10/1) (22 mL) was heated at 90 °C overnight. The reaction was diluted with water and extracted with EtOAc. The organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated to provide **8.3**, which was used in the next step without further purification.

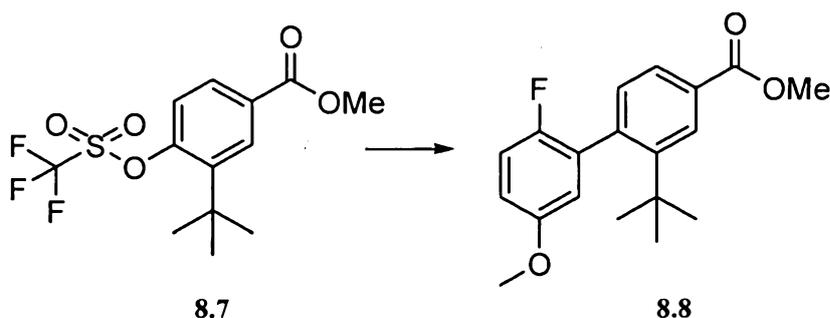


[0303] **Methyl (3S)-3-cyclopropyl-3-(3-hydroxyphenyl)propanoate and methyl (3R)-3-cyclopropyl-3-(3-hydroxyphenyl)propanoate (8.4 and 8.5).** To a flask containing **8.3** (1.2 g, 5.8 mmol) in MeOH (15 mL), was added H₂SO₄ (0.31 mL, 5.8 mmol). The resulting mixture was stirred overnight at reflux. The reaction was concentrated and then purified by combiflash (0 to 30% EtOAc/hexanes), and the enantiomers were resolved by chiral HPLC (Chiralcel OD-H column, 3% IPA/hexane, 220 nm) to afford **8.4** (40 minutes) and **8.5** (60 minutes).

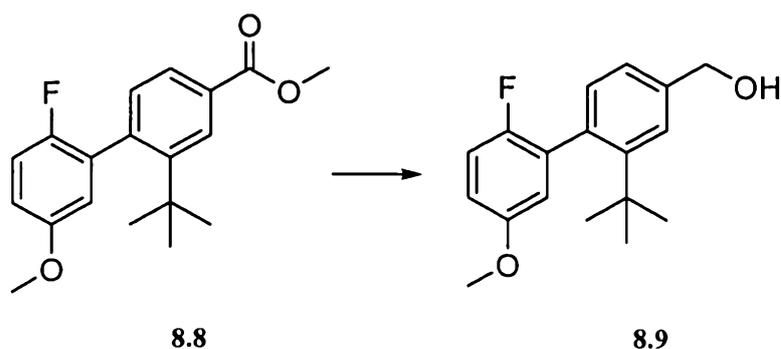


[0304] **Methyl 3-tert-butyl-4-(trifluoromethylsulfonyloxy)benzoate (8.7).** To a stirred solution of methyl 3-tert-butyl-4-hydroxybenzoate (available from Apin Chemical Ltd, United Kingdom)(0.100 g, 0.48 mmol) in DCM (10 mL, 155 mmol) at

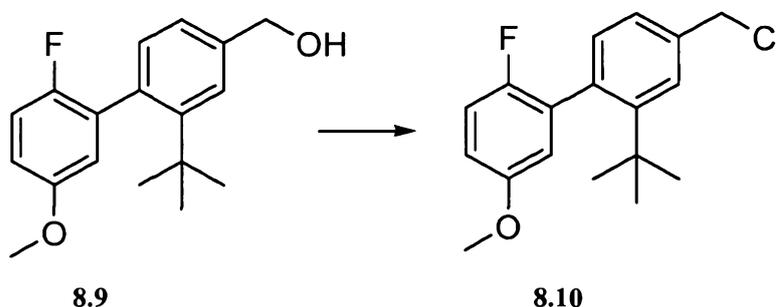
23°C, was added TEA (0.080 mL, 0.58 mmol) and DMAP (0.0059 g, 0.048 mmol), followed by triflic anhydride (0.097 mL, 0.58 mmol). The dark solution was stirred at room temperature and monitored by TLC and LC-MS. After 19 hours, the reaction was concentrated in vacuo. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-10% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **8.7** as a colorless oil (0.16g, 98%). MS ESI (pos.) m/e: 341.0 (M+H)⁺.



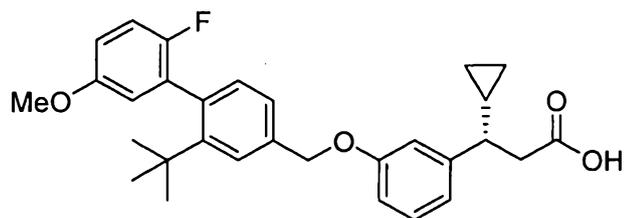
[0305] **Methyl 2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (8.8)**. To a stirred solution of **8.7** (0.100 g, 0.29 mmol) in DMF (2.00 mL, 26 mmol) at 23°C, was added 2-fluoro-5-methoxyphenylboronic acid (available from Aldrich)(0.100 g, 0.59 mmol), potassium carbonate (0.12 g, 0.88 mmol), followed by tetrakis(triphenylphosphine)palladium (0.034 g, 0.029 mmol). The mixture was heated to 100 °C. After 2 hours, the reaction was cooled to room temperature and diluted with water. The mixture was extracted with EtOAc (3 × 50mL) and concentrated in vacuo. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-15% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **8.8** as a colorless oil (0.85g, 71%). MS ESI (pos.) m/e: 317.2 (M+H)⁺.



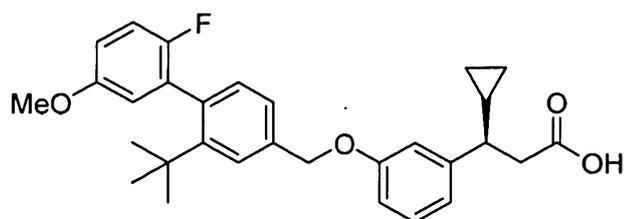
[0306] **(2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (8.9)**. To a cooled solution of **8.8** (0.85 g, 2.69 mmol) in dry THF (10.0 mL, 2.69 mmol) at 0°C, was added LAH (1.0 M solution in THF (6.0 mL, 6.0 mmol)). Upon complete addition, the reaction was allowed to warm to room temperature and monitored by TLC and LCMS. Upon completion, 1N NaOH (5 mL) was carefully added to quench the reaction. The resulting solution was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-40% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **8.9** as a colorless oil (0.56g, 72%). MS ESI (pos.) m/e: 311.2 (M+Na)⁺.



[0307] **4-(Chloromethyl)-2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (8.10)**. To a cooled solution of **8.9** (0.56 g, 1.93 mmol) in dry DCM (3.60 mL, 1.93 mmol) at 0°C, was added thionyl chloride (0.40 mL, 5.48 mmol) dropwise. Upon complete addition of thionyl chloride, the mixture was allowed to warm to room temperature. After 18 hours, the reaction was concentrated in vacuo. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-15% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **8.10** as a colorless solid (0.44g, 74%). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.56 (1 H, s), 7.25 (5 H, dd, J=7.7, 1.6 Hz), 7.01 (2 H, m), 6.86 (1 H, dd, J=9.0, 3.2 Hz), 6.77 (1 H, dd, J=5.9, 3.2 Hz), 4.65 (3 H, s), 3.79 (3 H, s), 1.24 (9 H, s).

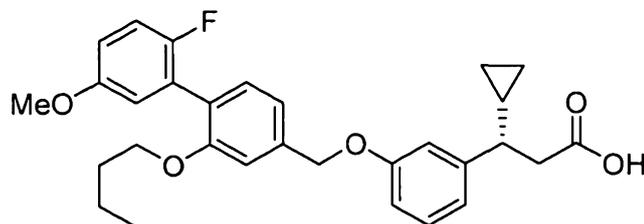


or

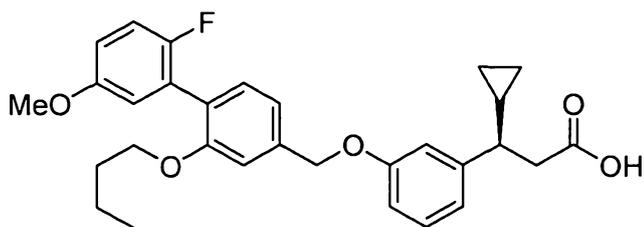


8

[0308] (3S)-3-Cyclopropyl-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (8). Example 8 was synthesized by a method analogous to the method used for compound 7 from 8.4 and 8.10. MS ESI (neg.) m/e: 475.2 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.62 (1 H, s), 7.24 - 7.32 (2 H, m), 6.98 - 7.08 (2 H, m), 6.84 - 6.92 (4 H, m), 6.78 (1 H, dd, J=5.9, 3.1 Hz), 5.09 (2 H, s), 3.79 (3 H, s), 2.80 (2 H, dd, J=7.6, 4.5 Hz), 2.38 (1 H, m), 1.25 (9 H, s), 1.04 (1 H, m), 0.60 (1 H, m), 0.44 (1 H, m), 0.30 (1 H, m), 0.17 (1 H, m).

[0309] Example 9

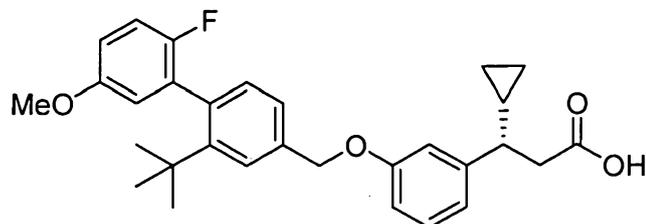
or



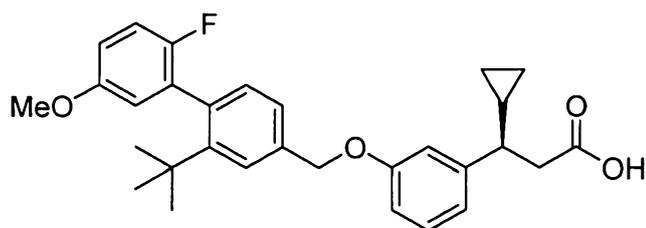
9

[0310] (3S)-3-(3-(((2-(Butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclopropylpropanoic acid or (3R)-3-(3-(((2-(butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclopropylpropanoic acid (9). Example 9 was synthesized analogous to the method for compound 7 from 8.4 and 5.4. MS ESI (neg.) m/e: 491.2 (M-H)⁻. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.23 - 7.31 (2 H, m), 7.01 - 7.09 (3 H, m), 6.82 - 6.92 (5 H, m), 5.08 (2 H, s), 4.00 (2 H, t, J=6.5 Hz), 3.81 (3 H, s), 2.79 (2 H, dd, J=7.2, 5.3 Hz), 2.35 - 2.41 (1 H, m), 1.64 - 1.71 (2 H, m), 1.34 - 1.43 (2 H, m), 0.98 - 1.08 (1 H, m), 0.90 (3 H, t, J=7.2 Hz), 0.56 - 0.63 (1 H, m), 0.45 (1 H, m), 0.27 - 0.34 (1 H, m), 0.14 - 0.20 (1 H, m).

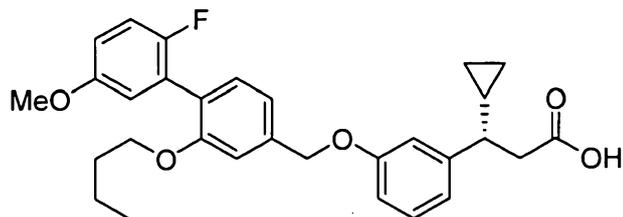
[0311]

Example 10

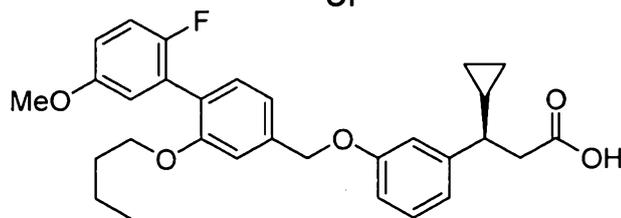
or

**10**

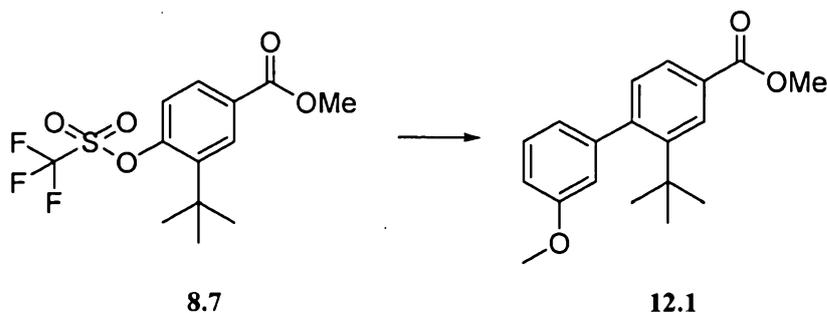
[0312] **(3R)-3-Cyclopropyl-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (10).** Example 10 was synthesized from 8.5 and 8.10 using a method analogous to the method used to prepare compound 7. MS ESI (neg.) m/e: 475.2 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.61 (1 H, m), 7.28 (2 H, m), 7.03 (2 H, m), 6.88 (4 H, m), 6.77 (1 H, m), 5.08 (2 H, s), 3.79 (3 H, s), 2.80 (2 H, m), 2.38 (1 H, m), 1.25 (9 H, s), 1.04 (1 H, m), 0.60 (1 H, m), 0.45 (1 H, m), 0.32 (1 H, m), 0.18 (1 H, m).

[0313] Example 11

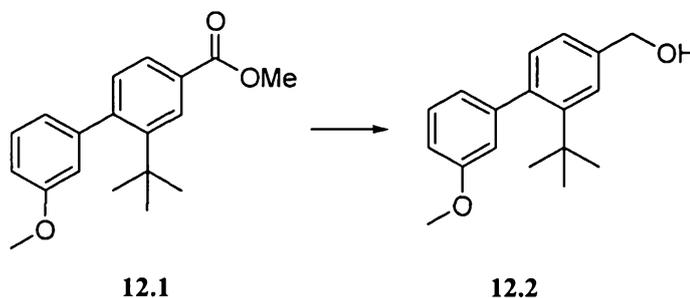
or

**11**

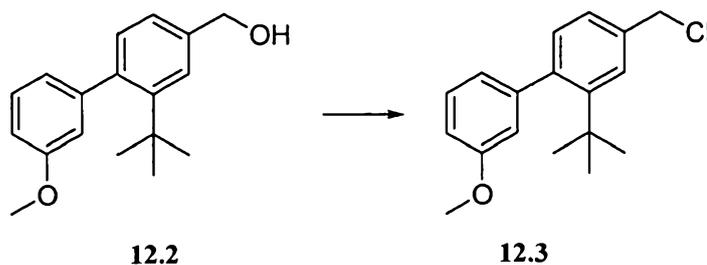
[0314] (3R)-3-(3-(((2-(Butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclopropylpropanoic acid or (3S)-3-(3-(((2-(butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclopropylpropanoic acid (**11**). Example 11 was synthesized from **8.5** and **5.4** using a method analogous to the method used to prepare compound **7**. MS ESI (neg.) m/e: 491.2 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.23 - 7.31 (2 H, m), 7.01 - 7.09 (3 H, m), 6.82 - 6.92 (5 H, m), 5.08 (2 H, s), 4.00 (2 H, t, J=6.5 Hz), 3.81 (3 H, s), 2.79 (2 H, dd, J=7.2, 5.3 Hz), 2.35 - 2.41 (1 H, m), 1.64 - 1.71 (2 H, m), 1.34 - 1.43 (2 H, m), 0.98 - 1.08 (1 H, m), 0.90 (3 H, t, J=7.2 Hz), 0.56 - 0.63 (1 H, m), 0.45 (1 H, m), 0.27 - 0.34 (1 H, m), 0.14 - 0.20 (1 H, m).

[0315] Example 12

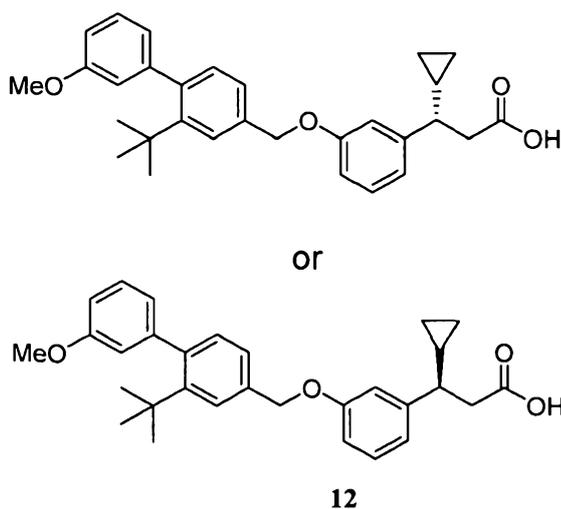
[0316] **Methyl 2-(1,1-dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-carboxylate (12.1)**. A dry round bottom flask containing **8.7** (1.40 g, 4.1 mmol), 3-methoxyphenylboronic acid (available from Aldrich)(1.27 g, 8.34 mmol), tetrakis(triphenylphosphine)palladium (0.49 g, 0.42 mmol), and potassium carbonate (1.71 g, 12.36 mmol) was evacuated and backfilled three times with argon. Dry DMF (12.0 mL) was added via syringe under argon, and the mixture was then heated to 100 °C and monitored by TLC. After 2 hours, the reaction was cooled to room temperature and diluted with water. The mixture was extracted three times with EtOAc and then concentrated under reduced pressure. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-15% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **12.1** as a colorless oil (1.01, 82%). MS ESI (pos.) m/e: 299.2 (M+H)⁺.



[0317] **(2-(1,1-Dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methanol (12.2)**. To a cooled solution of **12.1** (1.01 g, 3.38 mmol) in dry THF (10.0 mL) at 0°C, was added LAH (1.0 M solution in THF (6.7 mL, 6.7 mmol)). Upon complete addition, the reaction was allowed to warm to room temperature and monitored by TLC and LCMS. Upon completion, 1N NaOH (5 mL) was carefully added to quench the reaction. The resulting solution was extracted with EtOAc (3 × 10 mL), dried over MgSO₄, filtered and concentrated in vacuo. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-40% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **12.2** as a colorless oil (0.82, 90%). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.56 (1 H, s), 7.29 (1 H, t, J=3.8 Hz), 7.24 (1 H, m), 7.07 (1 H, d, J=7.6 Hz), 6.93 (2H, m), 6.86 (1H, d, J=1.5 Hz), 4.77 (2 H, s), 3.85 (3 H, s), 1.72 (1H, s), 1.26 (9 H, s).



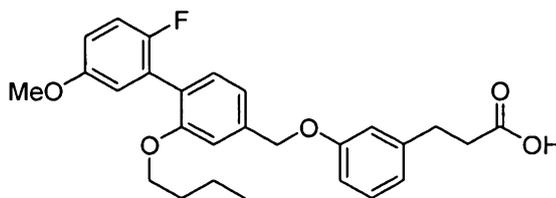
[0318] **4-(Chloromethyl)-2-(1,1-dimethylethyl)-3'-(methoxy)-1,1'-biphenyl (12.3).** A dry, round bottom flask containing **12.2** (0.82 g, 3.04 mmol) and DCM (8.5 mL) was cooled to 0°C. After 15 minutes, thionyl chloride (1.50 mL, 20.56 mmol) was carefully added dropwise at 0°C. Upon complete addition of thionyl chloride, the mixture was allowed to warm to room temperature and stirred overnight. After 25 hours, the reaction was concentrated under reduced pressure. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-15% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **12.3** as a colorless oil (0.82, 93%). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.53 (1 H, d, J= 1.7 Hz), 7.28 (3 H, m), 7.03 (1 H, d, J= 7.8 Hz), 6.90 (3 H, m), 4.65 (2H, s), 3.82 (3 H, s), 1.23 (9H, s).



[0319] **(3S)-3-Cyclopropyl-3-(3-(((2-(1,1-dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-(1,1-dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (12).** Compound **12** was synthesized from **8.4** and **12.3** by a method analogous to the method used to prepare compound **7**. MS ESI (neg.) m/e: 457.1 (M-H)⁺. ¹H NMR

(400 MHz, CDCl₃) δ ppm 7.58 (1 H, d, J=1.6 Hz), 7.23 - 7.27 (3 H, m), 7.05 (1 H, d, J=7.6 Hz), 6.82 - 6.92 (6 H, m), 5.07 (2 H, s), 3.81 (3 H, s), 2.79 (2 H, dd, J=7.4, 4.1 Hz), 2.37 (1 H, m), 1.22 (9 H, s), 1.03 (1 H, m), 0.59 (1 H, m), 0.43 (1 H, m), 0.30 (1 H, m), 0.16 (1 H, m).

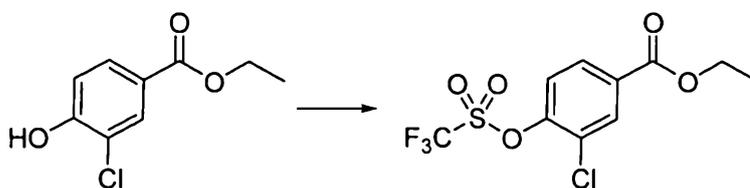
[0320] Example 13



13

[0321] 3-(3-(((2-(Butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (13). Compound 13 was synthesized from methyl 3-(3-hydroxyphenyl)propanoate (available from Agile Labs Division of Tyger Scientific) and 5.4 by a method analogous to the method used to prepare compound 7. ESI (neg.) m/e: 451.1 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.22 - 7.32 (2 H, m), 7.01 - 7.09 (3 H, m), 6.82 - 6.91 (5 H, m), 5.08 (2 H, s), 4.00 (2 H, t, J=6.5 Hz), 3.81 (3 H, s), 2.97 (2 H, t, J=7.8 Hz), 2.71 (2 H, t, J=7.8 Hz), 1.64 - 1.72 (2 H, m), 1.34 - 1.43 (2 H, m), 0.90 (3 H, t, J=7.3 Hz).

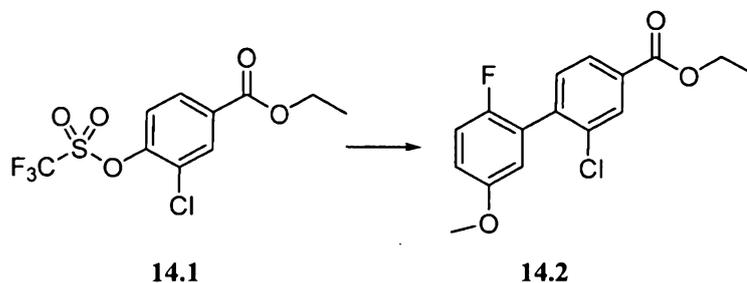
[0322] Example 14



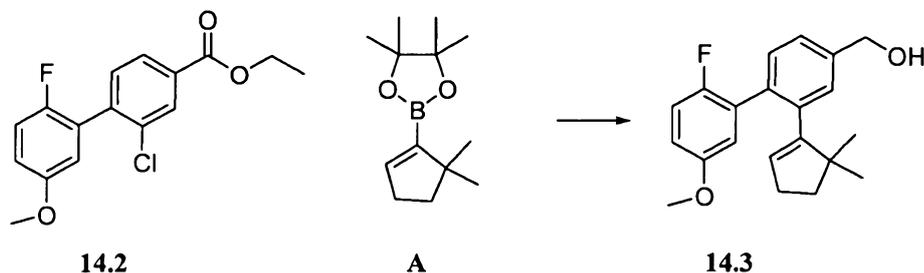
14.1

[0323] Ethyl 3-chloro-4-((trifluoromethyl)sulfonyl)oxybenzoate (14.1) A mixture of ethyl 3-chloro-4-hydroxybenzoate (available from Aldrich)(5.00 g, 25.0 mmol), N-phenyltriflimide (9.30 g, 26.0 mmol) and TEA (4.2 mL, 30.0 mmol) in DCM (40 mL) with a catalytic amount of DMAP, was stirred at ambient temperature overnight. DCM (150 mL) was added, and the reaction mixture was washed with brine (30 × 3 mL), dried over MgSO₄, and the solvent was removed under reduced pressure. The product

14.1 was used in the next step without further purification. MS ESI (pos.) m/e: 335.0 (M+Na)⁺.

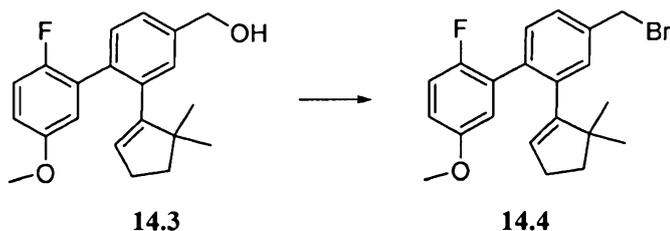


[0324] Ethyl 2-chloro-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (14.2) A reaction mixture of ethyl 3-chloro-4-(trifluoromethylsulfonyloxy)benzoate **14.1** (3.00g, 9.02 mmol), 2-fluoro-5-methoxyphenylboronic acid (available from Aldrich)(1.84 g, 10.8 mmol), (t-4)-tetrakis(triphenylphosphine)palladium (0.521 g, 0.451 mmol) and potassium carbonate (2.49 g, 18.0 mmol) in DMF (20 mL), was purged with N₂ three times and then heated at 100 °C for 4 hours. The reaction was cooled to room temperature, and EtOAc (130 mL) was added. The mixture was then washed with brine (30 × 4 mL). The organic layer was dried over MgSO₄. The residue was purified by Combiflash silica gel column (eluant with hexane/EtOAc; 85/15) to give **14.2**. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.08 (d, 1H), 7.90 (d, 1H), 7.33 (dd, 1H), 6.96 - 7.02 (m, 1H), 6.82 - 6.85 (m, 1H), 6.74 (d, 1H), 4.33 (q, 2H), 4.31 (s, 3H), 1.34 (t, 3H). MS ESI (pos.) m/e: 309.1 (M+H)⁺.

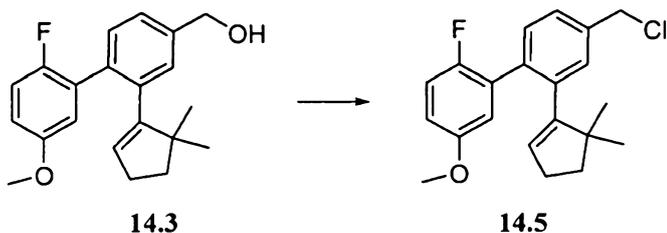


[0325] (2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (14.3) A reaction mixture of compound **14.2** (1.80 g, 5.80 mmol), 2-(5,5-dimethylcyclopent-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **A** (1.40 g, 6.4 mmol), S-Phos (0.48 g, 1.20 mmol), tripotassium phosphate (3.10 g, 15.0 mmol) and palladium acetate (0.13 g, 0.58 mmol) in DMF (10.0 mL) and water (1.0 mL), was purged with N₂ three times. The resulting mixture was heated at 100 °C overnight. EtOAc (120 mL) was added, and the mixture was washed with brine (25 × 2 mL). The

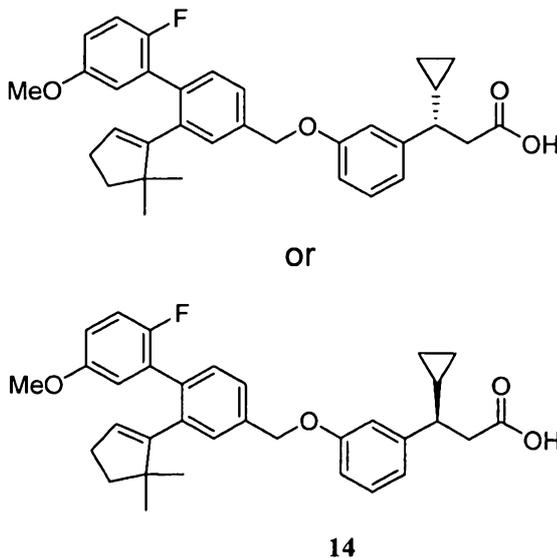
organic layer was dried with MgSO₄. The residue was purified by Combiflash silica gel, eluant with hexane/EtOAc, 9/1 to give Suzuki coupling product as an intermediate, ethyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate. MS ESI (pos.) m/e: 369.1 (M+H)⁺. To a solution of ethyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (1.00 g, 3.0 mmol) in THF (10.0 mL), was slowly added LAH, (1.0M solution in diethyl ether, 4.0 mL, 4.0 mmol) at 0 °C. After the addition, the reaction mixture was stirred at 40 °C for 1.5 hours, and then at room temperature for 2 hours. A mixture of water (0.22 mL) in THF (2.0 mL) was slowly added and then 15% sodium hydroxide (0.22 mL) was added at 0 °C. Finally, water (0.65 mL) was added at room temperature. The solid was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by Combiflash (silica gel column, eluant with hexane/EtOAc, 90/10 to 70/30) to give the title compound **14.3**. ¹H NMR (400 MHz, CDCl₃) δ ppm. 7.24 (s, 2H), 7.09 - 7.21 (m, 1H), 6.84 - 6.96 (m, 1H), 6.68-6.72 (m, 2H), 5.43 (s, 1H), 4.65 (s, 2H), 3.66 (s, 3H), 2.17 (td, 2H), 1.77 (b, 1H), 1.58 (t, 2H), 0.78 (s, 6H). MS ESI (pos.) m/e: 309.1 (M-HO)⁺, 345.2 (M+H₃O)⁺.



[0326] 4-(Bromomethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (14.4) To a solution of triphenylphosphine (0.13 g, 0.51 mmol) in DCM (1.0 mL), was slowly added bromine (0.081 g, 0.51 mmol, 0.25 mL, 2M in CCl₄) at 0°C. The resulting mixture was stirred at 0°C for 15 minutes and then a mixture of compound **14.3** (0.15g, 0.46 mmol) and anhydrous pyridine (0.041 mL, 0.51 mmol) in DCM (3.0 mL) was added to the mixture. The reaction mixture was stirred at room temperature for 2 hours. DCM (80 mL) was added, and the mixture was washed with water (20 × 2 mL), and dried over Na₂SO₄. The solvent was removed under reduced pressure. The crude product **14.4** was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ ppm. 7.16 - 7.29 (m, 3H), 6.88 (t, 1H), 6.72 (m, 2 H), 5.45 (s, 1H), 4.46 (s, 2 H), 3.68 (s, 3H), 2.16-2.19 (m, 2H), 1.59 (t, 2H), 0.78 (s, 6H).



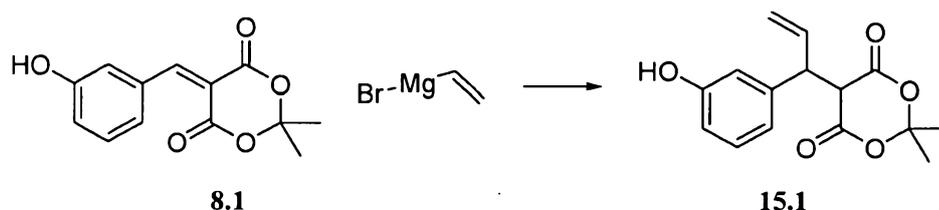
4-(Chloromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (14.5) To a solution of compound **14.3** (1.10 g, 3.37 mmol) and a catalytic amount of DMF (0.10 mL) in DCM (12.0 mL), was slowly added thionyl chloride (0.802 g, 6.74 mmol) at 0 °C. After addition, the reaction mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure, and the resulting residue was purified by Combiflash (silica gel column eluted with hexane/EtOAc, 100/0 to 95/5) to give the title compound **14.5** (1.15g). ¹H NMR (400 MHz, CDCl₃) δ ppm. 7.32 - 7.39 (m, 2H), 7.28-7.29 (m, 1H), 6.88 (t, 1H), 6.80-6.82 (m, 2 H), 5.56 (s, 1H), 4.66 (s, 2 H), 3.78 (s, 3H), 2.27-2.29 (m, 2H), 1.69 (t, 2H), 0.89 (s, 6H).



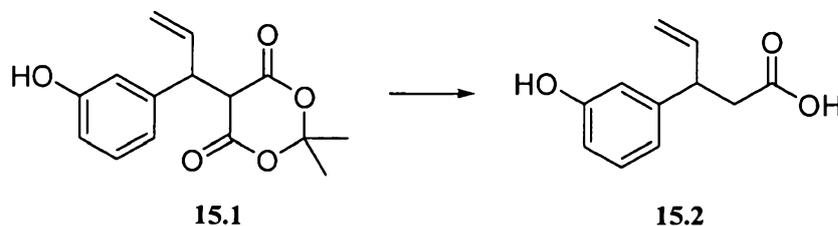
[0327] (3S)-3-Cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (14). Compound **14** was synthesized from **8.4** and **14.5** by a method analogous to that used to prepare compound **7**. ESI (neg.) m/e: 513.3 (M-H)⁻. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.39 - 7.42 (1 H,

m), 7.30 - 7.36 (2 H, m), 7.23 - 7.28 (2 H, m), 6.97 (1 H, m), 6.84 - 6.91 (3 H, m), 6.80 (2 H, ddd, $J=6.1, 2.5, 2.3$ Hz), 5.53 (1 H, s), 5.10 (2 H, s), 3.75 - 3.81 (3 H, m), 2.79 (2 H, dd, $J=7.2, 4.5$ Hz), 2.38 (1 H, m), 2.25 (2 H, m), 1.66 (2 H, t, $J=7.0$ Hz), 0.97 - 1.07 (1 H, m), 0.86 (6 H, s), 0.56 - 0.63 (1 H, m), 0.44 (1 H, m), 0.27 - 0.33 (1 H, m), 0.13 - 0.20 (1 H, m).

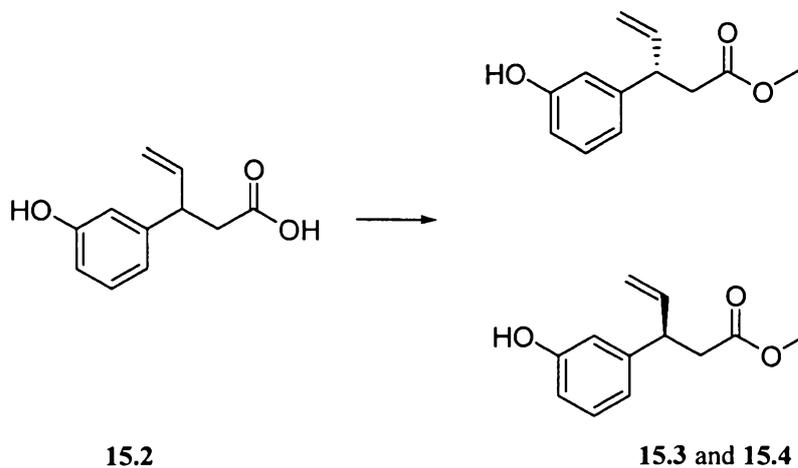
[0328] **Example 15**



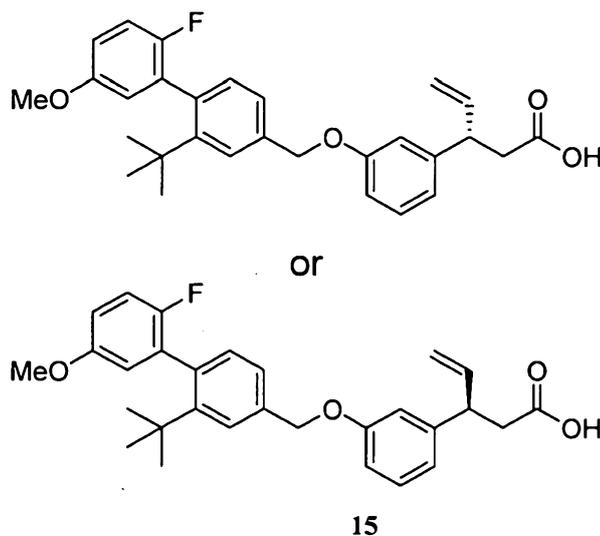
[0329] **5-(1-(3-Hydroxyphenyl)-2-propenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (15.1).** To a solution of **8.1** (6.0 g, 24.17 mmol) in THF, was added vinylmagnesium bromide (available from Aldrich)(207.2 mL, 145.0 mmol) via cannula at 0 °C. The resulting heterogeneous mixture was warmed to room temperature, stirred for 30 minutes, and quenched with 1 N aq. HCl. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated to provide **15.1** as a yellow oil which was used in the next step without further purification.



[0330] **3-(3-Hydroxyphenyl)-4-pentenoic acid (15.2).** **8.1** in DMF/water (10/1) (66 mL) was overnight heated at 90 °C. The reaction was diluted with water and extracted with EtOAc. The organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated to provide compound **15.2**.



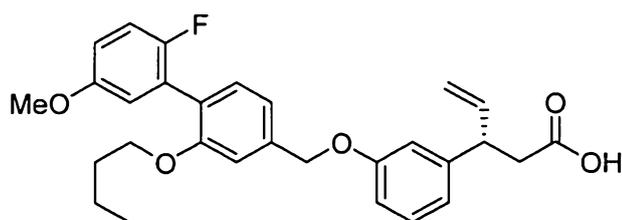
[0331] **Methyl (3S)-3-(3-hydroxyphenyl)-4-pentenoate and methyl (3R)-3-(3-hydroxyphenyl)-4-pentenoate (15.3 and 15.4).** To flask containing 15.2 in MeOH (50 mL), was added H₂SO₄ (0.0129 mL, 0.242 mmol). The resulting mixture was stirred at reflux overnight. The reaction was concentrated and then purified by combiflash (0 to 30% EtOAc/ Hexanes). The enantiomers were resolved by chiral HPLC (Chiralcel OD-H column, 3% IPA/hexane, 220 nm wavelength used to observe the compound peaks) to afford 15.3 (0.400 g, 16.0% yield from 8.1) (28 minutes) and 15.4 (0.400 g, 16.0% yield from 8.1) (45 minutes).



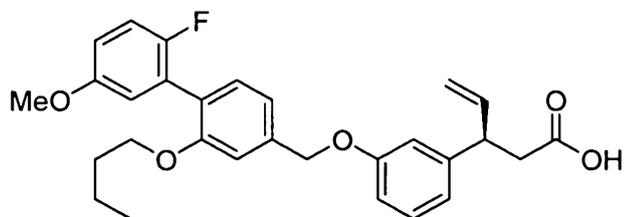
[0332] **(3S)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-pentenoic acid or (3R)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-**

pentenoic acid (15). Compound 15 was synthesized from 15.3 and 8.10 by a method analogous to that used to prepare compound 7. ESI (neg.) m/e: 461.2 (M-H)⁺. ¹H NMR (500 MHz, CDCl₃) δ ppm 7.61 (1 H, s), 7.30 (1 H, dd, J=7.7, 1.1 Hz), 7.27 (1 H, m), 6.99 - 7.07 (2 H, m), 6.85 - 6.92 (4 H, m), 6.79 (1 H, dd, J=5.9, 3.2 Hz), 5.98 (1 H, m), 5.08 - 5.14 (4 H, m), 3.87 (1 H, m), 3.80 (3 H, s), 2.79 (2 H, t, J=7.5 Hz), 1.25 (9 H, s).

[0333] Example 16



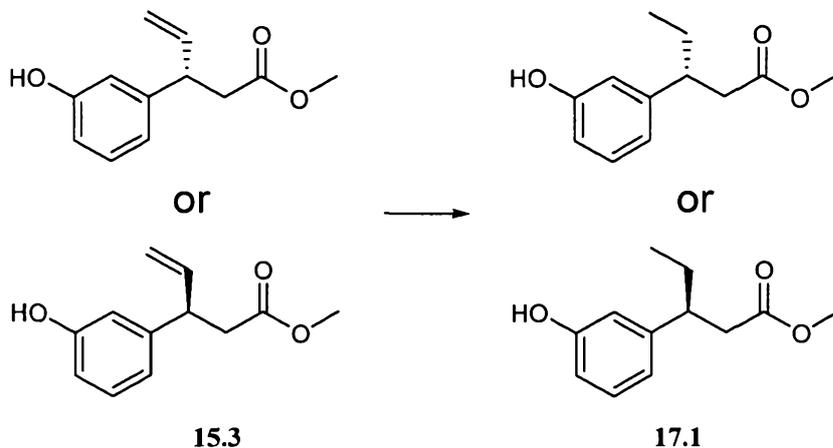
or



16

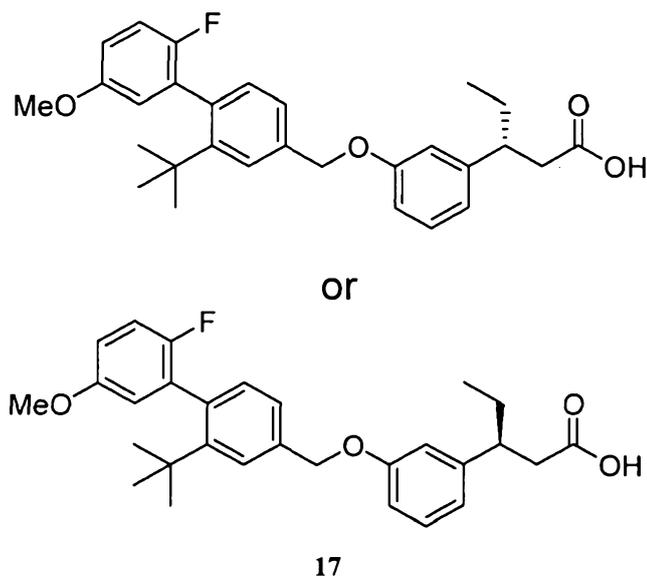
[0334] (3S)-3-(3-(((2-(Butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-pentenoic acid or (3R)-3-(3-(((2-(butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-pentenoic acid (16). Compound 16 was synthesized from 15.3 and 5.4 by a method analogous to that used to prepare compound 7. ESI (neg.) m/e: 477.2 (M-H)⁺. ¹H NMR (500 MHz, CDCl₃) δ ppm 7.24 - 7.31 (2 H, m), 7.01 - 7.09 (3 H, m), 6.83 - 6.90 (5 H, m), 5.99 (1 H, ddd, J=17.4, 10.1, 7.0 Hz), 5.07 - 5.14 (4 H, m), 4.00 (2 H, t, J=6.4 Hz), 3.83 - 3.89 (1 H, m), 3.81 (3 H, s), 2.74 - 2.84 (2 H, m), 1.65 - 1.71 (2 H, m), 1.35 - 1.42 (2 H, m), 0.90 (3 H, t, J=7.3 Hz).

[0335]

Example 17

[0336]

Methyl (3R)-3-(3-hydroxyphenyl)pentanoate or methyl (3S)-3-(3-hydroxyphenyl)pentanoate (17.1). A 50 mL flask containing a solution of 15.3 (100 mg, 485 μmol) in EtOAc (10 mL) was purged with N_2 . To the flask was added palladium, 10 wt. % (dry), on carbon powder, wet (103 mg, 97.0 μmol). The flask was then purged with H_2 , and the contents were stirred overnight under a H_2 balloon. The black mixture was filtered through a pad of Celite and concentrated to afford a pink oil. The crude product was purified by combiflash (0 to 10% EtOAc/hexanes) yielding 17.1.

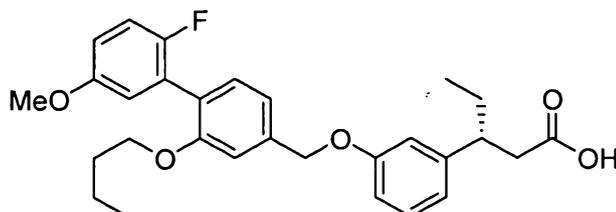


[0337]

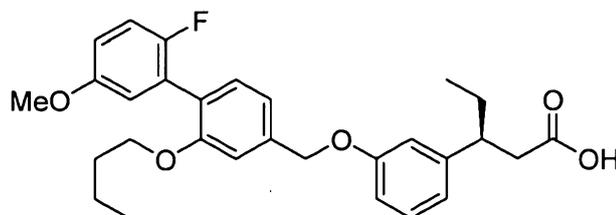
(3R)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-(1,1-

dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid (17). Compound 17 was synthesized from 17.1 and 8.10 using a method analogous to that used to prepare compound 7. EI (neg.) m/e: 463.1 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.62 (1 H, d, J=1.6 Hz), 7.23 - 7.32 (3 H, m), 7.03 (2 H, m), 6.81 - 6.90 (4 H, m), 6.78 (1 H, dd, J=6.0, 3.2 Hz), 5.08 (2 H, s), 3.79 (3 H, s), 3.00 (1 H, m), 2.65 (2 H, dd, J=7.3, 4.6 Hz), 1.74 (1 H, m), 1.62 (1 H, m), 1.25 (9 H, s), 0.81 (3 H, t, J=7.3 Hz).

[0338] **Example 18**

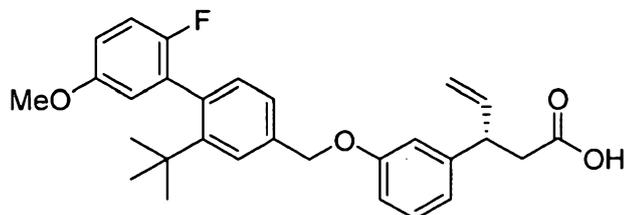


or

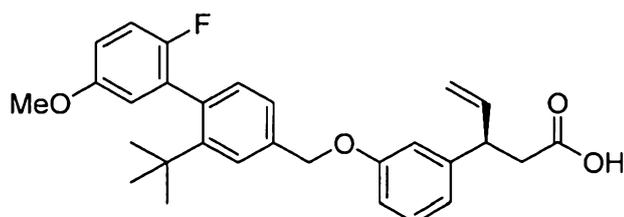


18

[0339] **(3R)-3-(3-(((2-(Butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-(butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid (18).** Compound 18 was synthesized from 17.1 and 5.4 by a method analogous to that used to prepare compound 7. ESI (neg.) m/e: 479.2 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.22 - 7.31 (3 H, m), 7.01 - 7.09 (3 H, m), 6.81 - 6.90 (5 H, m), 5.08 (2 H, s), 4.00 (2 H, t, J=6.6 Hz), 3.81 (3 H, s), 2.96 - 3.03 (1 H, m), 2.65 (2 H, dd, J=7.4, 5.7 Hz), 1.63 - 1.74 (3 H, m), 1.34 - 1.43 (2 H, m), 0.90 (3 H, t, J=7.3 Hz), 0.81 (3 H, t, J=7.3 Hz).

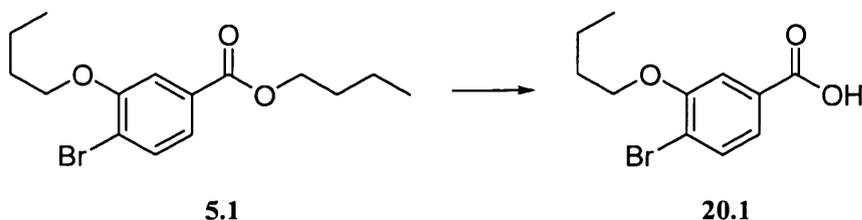
[0340] Example 19

or



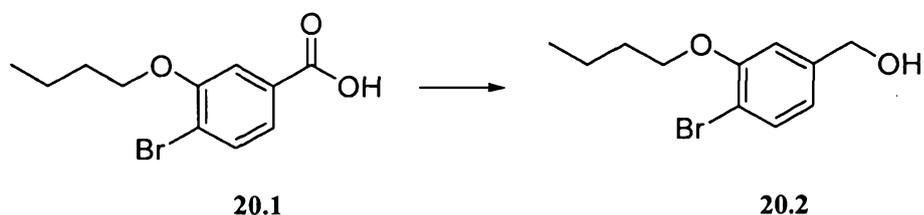
19

[0341] (3R)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-pentenoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-pentenoic acid (19). Compound 19 was synthesized from 15.4 and 8.10 by a method analogous to that used to prepare compound 7. ESI (neg.) m/e: 460.7 (M-H)⁺. ¹H NMR (500 MHz, CDCl₃) δ ppm 7.61 (1 H, s), 7.30 (1 H, dd, J=7.7, 1.1 Hz), 7.27 (1 H, m), 6.99 - 7.07 (2 H, m), 6.85 - 6.92 (4 H, m), 6.79 (1 H, dd, J=5.9, 3.2 Hz), 5.98 (1 H, m), 5.08 - 5.14 (4 H, m), 3.87 (1 H, m), 3.80 (3 H, s), 2.79 (2 H, t, J=7.5 Hz), 1.25 (9 H, s).

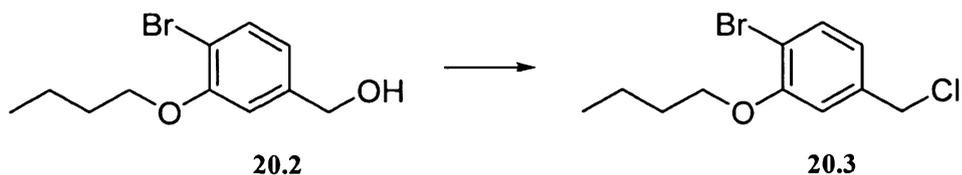
[0342] Example 20

[0343] 4-Bromo-3-(butyloxy)benzoic acid (20.1). To a solution of 5.1 (0.90 g, 2.7 mmol) in THF/MeOH (2/1) (18 mL), was added lithium hydroxide (6.0 mL, 6.0 mmol). The resulting mixture was stirred overnight at 23 °C and then quenched with excess 1N HCl. The mixture was then extracted with EtOAc. The combined organic

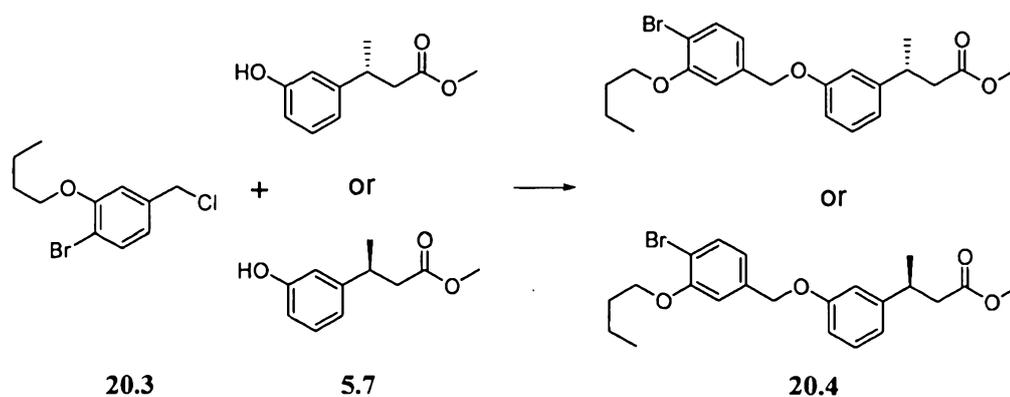
layers were dried over Na_2SO_4 and concentrated. The crude residue was purified by combiflash (0 to 40% EtOAc/hexanes) to afford a **20.1** (0.68 g, 91% yield).



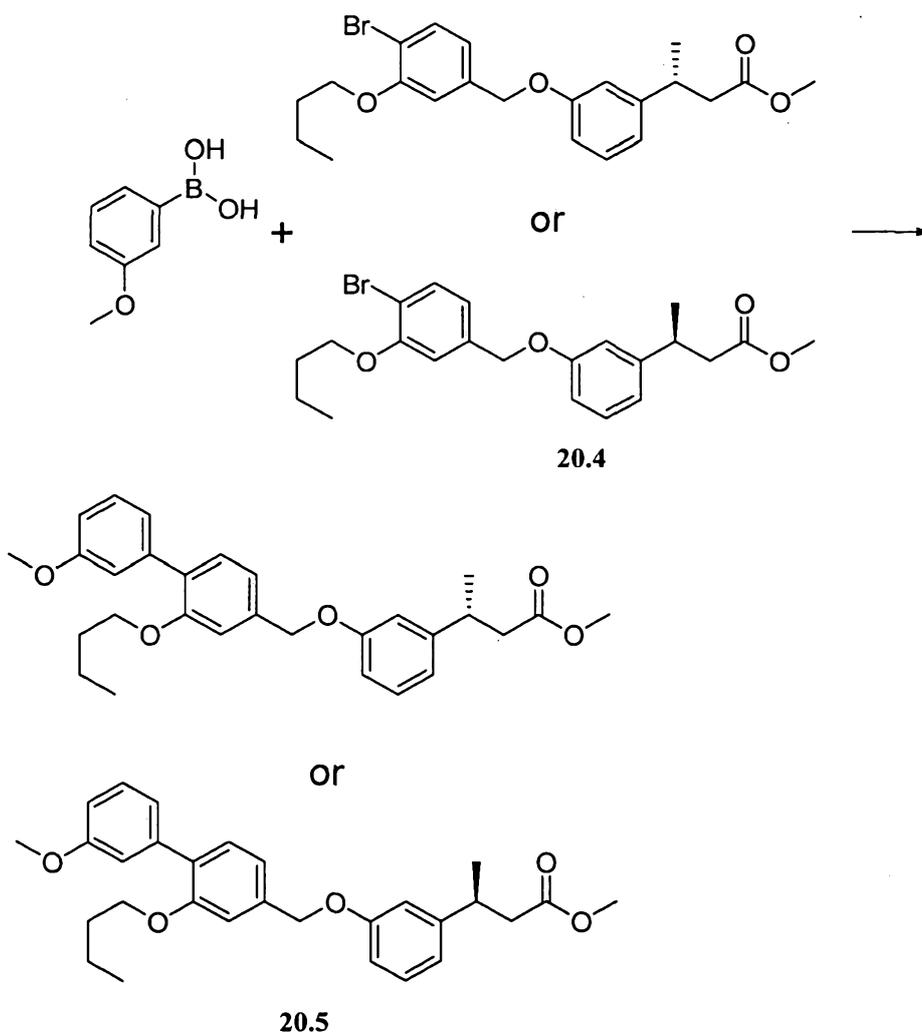
[0344] **(4-Bromo-3-(butyloxy)phenyl)methanol (20.2)**. A solution of **20.1** (0.68 g, 2490 μmol) in THF (5 mL) was treated with borane THF complex (4979 μL , 4979 μmol) and stirred overnight at 65 °C. The reaction mixture was quenched with MeOH, diluted with EtOAc, and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by combiflash (10 to 50% EtOAc/hexanes) yielding **20.2** (659.3 mg, 102% yield).



[0345] **2-Bromo-5-(chloromethyl)phenyl butyl ether (20.3)**. To a stirred solution of **20.2** (659.3 mg, 2544 μmol) in DCM (15 mL) at 23 °C, was added thionyl chloride (371 μL , 5088 μmol). The resulting mixture was stirred overnight. The reaction was concentrated and then purified by combiflash (0 to 10% EtOAc/ Hexanes) to provide **20.3** (650mg, 92.0% yield).

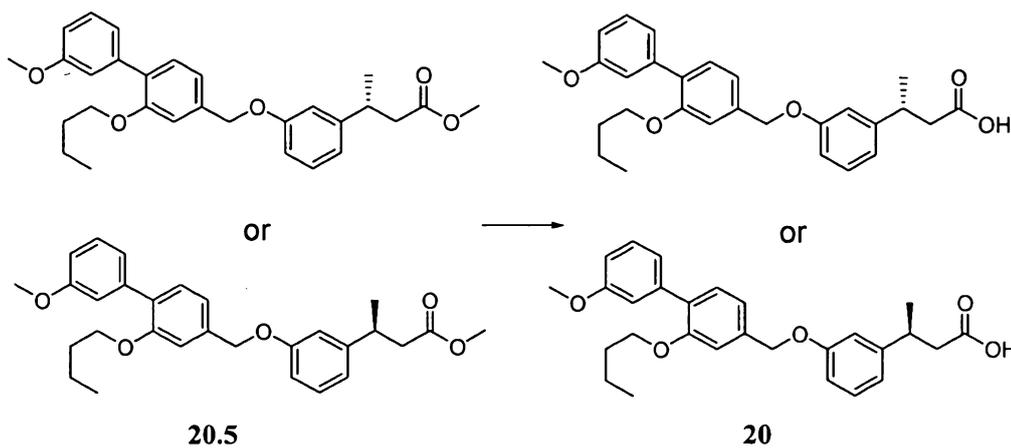


[0346] **Methyl (3R)-3-(3-(((4-bromo-3-(butyloxy)phenyl)methyl)oxy)phenyl)butanoate or methyl (3S)-3-(3-(((4-bromo-3-(butyloxy)phenyl)methyl)oxy)phenyl)butanoate (20.4).** To a flask containing **5.7** (125.0 g, 643.6 mmol) and cesium carbonate (272.6 g, 836.6 mmol) in DMF (1 mL), was added **20.3** (214.4 g, 772.3 mmol), and the resulting mixture was stirred overnight. The reaction was diluted with water and extracted with EtOAc. The organic layers were washed with brine, dried over Na₂SO₄, filtered, concentrated, and then purified by combiflash (0 to 20% EtOAc/ Hexanes) to provide **20.4**.

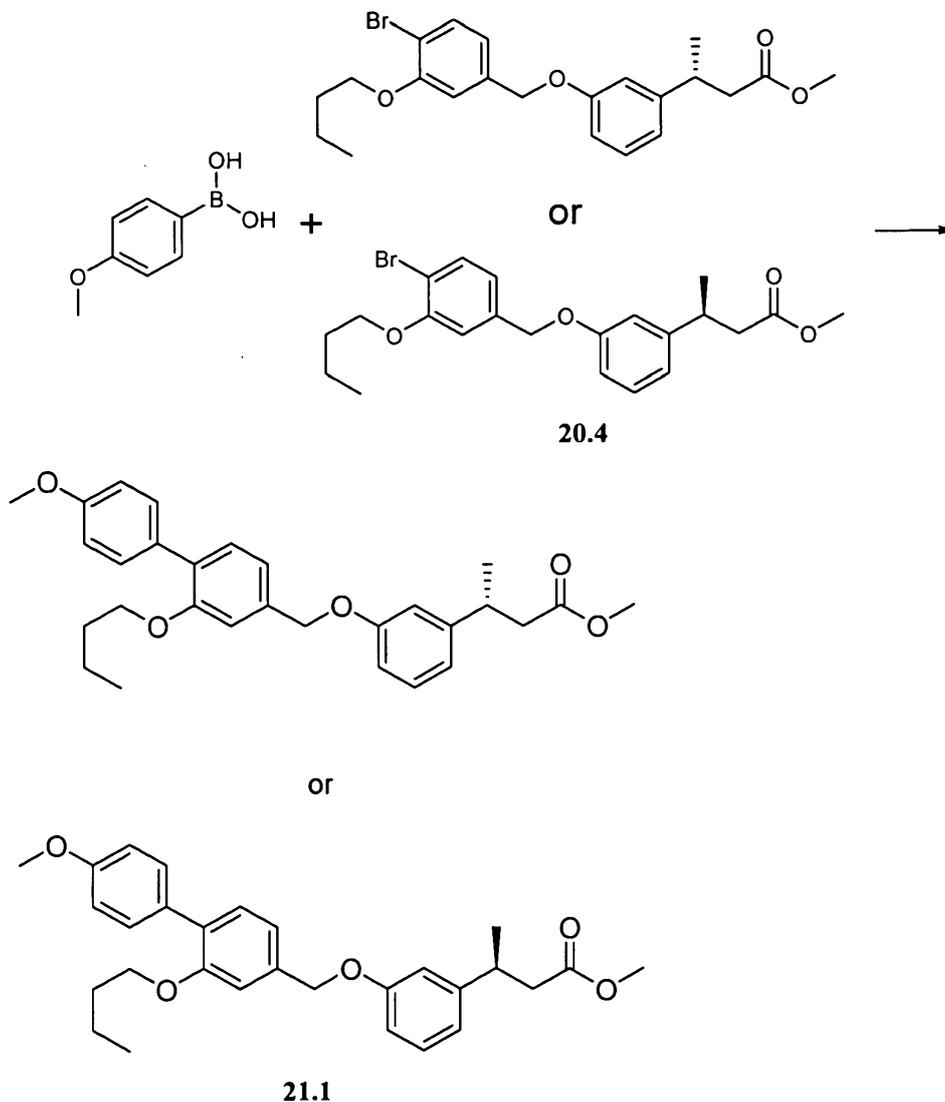


[0347] **Methyl (3R)-3-(3-(((2-(butyloxy)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate or methyl (3S)-3-(3-(((2-(butyloxy)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate (20.5).** To a 2 dram vial charged with

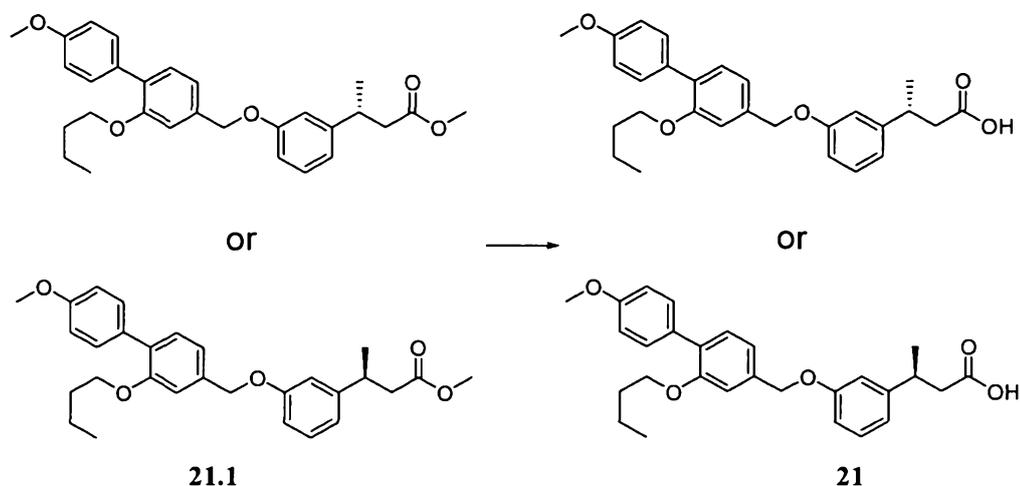
20.4 (25.0 mg, 57.4 μmol), tetrakis(triphenylphosphine)palladium (0) (13.3 mg, 11.5 μmol), cesium fluoride (10.6 μL , 287 μmol), and 3-methoxybenzeneboronic acid (available from Aldrich)(26.2 mg, 172 μmol), was added DME (1 mL). The resulting mixture was then heated at 85 °C overnight. The reaction was allowed to cool and then filtered and concentrated. The crude product was purified by combiflash (0 to 20% EtOAc/ hexanes) yielding **20.5**.



[0348] **(3R)-3-(3-(((2-(Butyloxy)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(butyloxy)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (20)**. To a solution of **20.5** (26.6 mg, 57.4 μmol) in THF/MeOH (2/1) (1.5 mL), was added lithium hydroxide (0.500 mL, 500 μmol). The resulting mixture was stirred overnight at 23 °C, quenched with excess 1N HCl, and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude residue was purified by combiflash (0 to 40% EtOAc/hexanes) to afford **20** (16.2 mg, 62.9% yield). ESI (neg.) m/e: 446.8 (M-H)⁻. ¹H NMR (500 MHz, CDCl_3) δ ppm 7.34 (2 H, m), 7.23 - 7.26 (1 H, m), 7.13 - 7.15 (2 H, m), 7.07 - 7.09 (2 H, m), 6.89 - 6.91 (2 H, m), 6.85 - 6.88 (2 H, m), 5.07 (2 H, s), 4.00 (2 H, t, J=6.5 Hz), 3.85 (3 H, s), 3.24 - 3.31 (1 H, m), 2.67 - 2.72 (1 H, m), 2.56 - 2.62 (1 H, m), 1.70 - 1.76 (2 H, m), 1.41 - 1.48 (2 H, m), 1.34 (3 H, d, J=7.1 Hz), 0.93 (3 H, t, J=7.3 Hz).

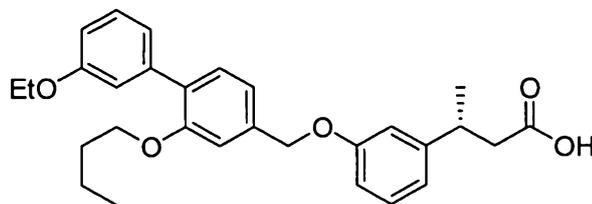
[0349] Example 21

[0350] Methyl (3R)-3-(3-(((2-(butyloxy)-4'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate or methyl (3S)-3-(3-(((2-(butyloxy)-4'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate (21.1). To a 2 dram vial charged with **20.4** (25.0 mg, 57.4 μmol), tetrakis(triphenylphosphine)palladium(0) (13.3 mg, 11.5 μmol), cesium fluoride (10.6 μL , 287 μmol), and 4-methoxyphenylboronic acid (available from Aldrich)(26.2 mg, 172 μmol), was added DME (1 mL). The resulting mixture was then heated at 85°C overnight. The reaction was allowed to cool and then filtered and concentrated. The crude product was purified by combiflash (0 to 20% EtOAc/ hexanes) yielding **21.1**.

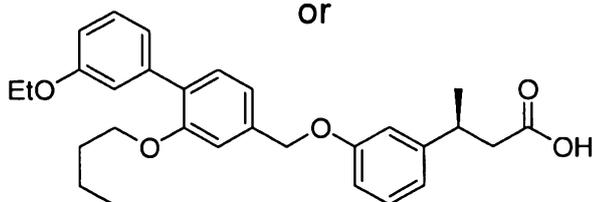


[0351] (3R)-3-(3-(((2-(Butyloxy)-4'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(butyloxy)-4'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (**21**). To a solution of **21.1** (26.6 mg, 57.4 μmol) in THF/MeOH (2/1) (1.5 mL) was added lithium hydroxide (0.500 mL, 500 μmol). The resulting mixture was stirred overnight at 23 °C, quenched with excess 1N HCl, and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude residue was purified by combiflash (5 to 25% EtOAc/hexanes) to afford **21** (19.3 mg, 75.0% yield). ESI (neg.) m/e: 446.8 (M-H)⁻. ¹H NMR (400 MHz, CDCl_3) δ ppm 7.49 - 7.53 (2 H, m), 7.33 (1 H, d, J=8.2 Hz), 7.23 - 7.26 (1 H, m), 7.05 - 7.08 (2 H, m), 6.85 - 6.98 (5 H, m), 5.06 (2 H, s), 4.00 (2 H, t, J=6.5 Hz), 3.86 (3 H, s), 3.23 - 3.32 (1 H, m), 2.68 (1 H, m), 2.55 - 2.62 (1 H, m), 1.69 - 1.76 (2 H, m), 1.40 - 1.49 (2 H, m), 1.34 (3 H, d, J=7.0 Hz), 0.94 (3 H, t, J=7.3 Hz).

[0352]

Example 22

or

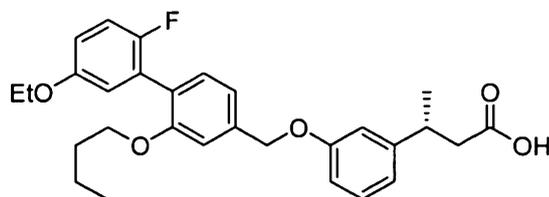


22

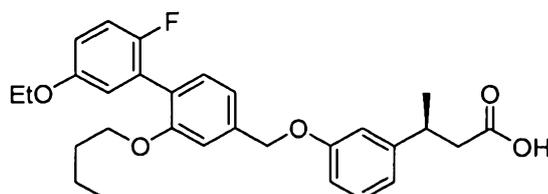
[0353]

(3R)-3-(3-(((2-(Butyloxy)-3'-(ethoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(butyloxy)-3'-(ethoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (22). Compound 22 was synthesized from 20.4 by a method analogous to that used to prepare compound 21. 3-Ethoxyphenylboronic acid is available from Aldrich. ESI (neg.) m/e: 460.7 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.36 - 7.39 (1 H, m), 7.25 - 7.34 (2 H, m), 7.08 - 7.16 (4 H, m), 6.87 - 6.93 (4 H, m), 5.09 (2 H, s), 4.10 (2 H, q, J=7.0 Hz), 4.01 (2 H, t, J=6.5 Hz), 3.25 - 3.33 (1 H, m), 2.68 - 2.74 (1 H, m), 2.57 - 2.64 (1 H, m), 1.70 - 1.78 (2 H, m), 1.41 - 1.50 (5 H, m), 1.35 (3 H, d, J=6.8 Hz), 0.94 (3 H, t, J=7.4 Hz).

[0354]

Example 23

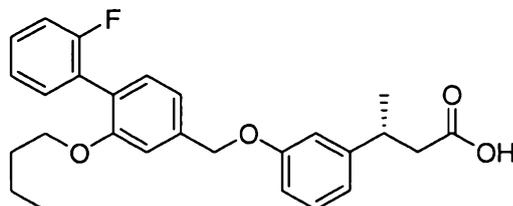
or



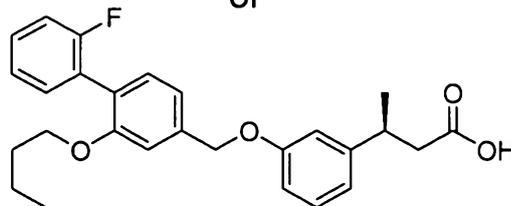
23

[0355] **(3R)-3-(3-(((2-(Butyloxy)-5'-(ethyloxy)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(butyloxy)-5'-(ethyloxy)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (23).** Compound 23 was synthesized from 20.4 by a method analogous to that used to prepare compound 21. ESI (neg.) m/e: 478.7 (M-H)⁺. ¹H NMR (500 MHz, CDCl₃) δ ppm 7.23 - 7.31 (3 H, m), 7.00 - 7.09 (3 H, m), 6.82 - 6.91 (5 H, m), 5.08 (2 H, s), 3.98 - 4.05 (4 H, m), 3.24 - 3.31 (1 H, m), 2.66 - 2.72 (1 H, m), 2.56 - 2.62 (1 H, m), 1.65 - 1.70 (2 H, m), 1.36 - 1.43 (5 H, m), 1.34 (3 H, d, J=6.8 Hz), 0.87 - 0.92 (3 H, m).

[0356] **Example 24**



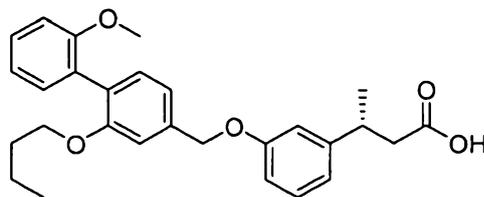
OR



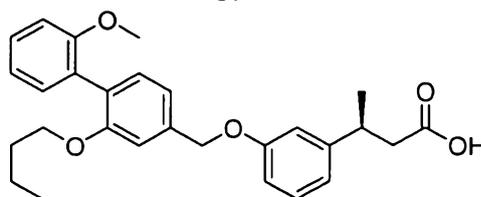
24

[0357] **(3R)-3-(3-(((2-(Butyloxy)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(butyloxy)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (24).** Compound 24 was synthesized from 20.4 by a method analogous to that used to prepare compound 21. 2-Fluorophenylboronic acid is available from Aldrich. ESI (neg.) m/e: 434.8 (M-H)⁺. ¹H NMR (500 MHz, CDCl₃) δ ppm 7.29 - 7.38 (3 H, m), 7.24 - 7.27 (2 H, m), 7.18 (1 H, td, J=7.5, 1.1 Hz), 7.07 - 7.14 (3 H, m), 6.89 (2 H, m), 6.87 (1 H, m), 5.08 (2 H, s), 4.00 (2 H, t, J=6.4 Hz), 3.24 - 3.32 (1 H, m), 2.66 - 2.72 (1 H, m), 2.55 - 2.62 (1 H, m), 1.63 - 1.69 (2 H, m), 1.32 - 1.40 (5 H, m), 0.89 (3 H, t, J=7.3 Hz).

[0358]

Example 25

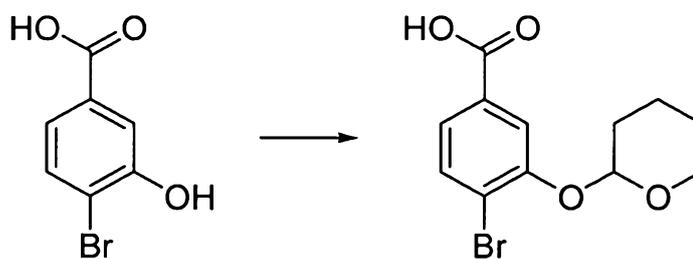
or

**25**

[0359]

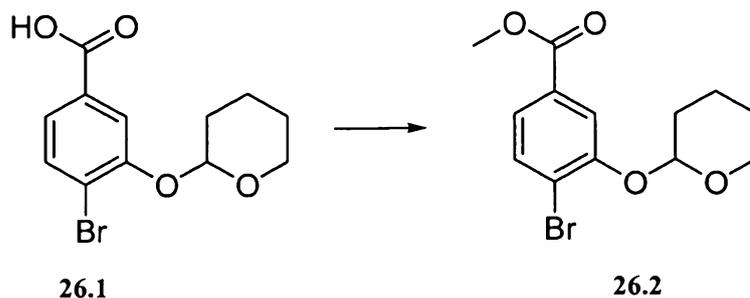
(3R)-3-(3-(((2-(Butyloxy)-2'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(butyloxy)-2'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (25). Compound **25** was synthesized from **20.4** by a method analogous to that used to prepare compound **21**. 2-Methoxyphenylboronic acid is available from Aldrich. ESI (neg.) m/e: 446.8 (M-H)⁺.

[0360]

Example 26**26.1**

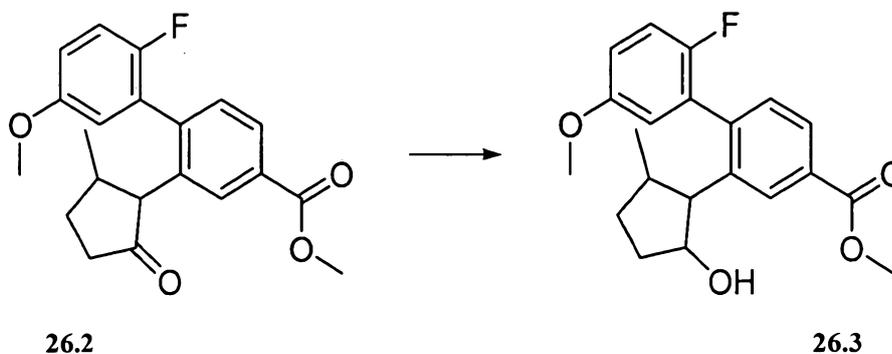
[0361]

4-Bromo-3-(tetrahydro-2H-pyran-2-yloxy)benzoic acid 4-bromo-3-(tetrahydro-2H-pyran-2-yloxy)benzoic acid (26.1). To solution of 4-bromo-3-hydroxybenzoic acid (available from Combi-Blocks Inc.)(2.50 g, 11.5 mmol) in DCM (100 mL) at 23 °C, was added 3,4-dihydro-2H-pyran (available from Aldrich)(2.10 mL, 23.0 mmol) followed by PPTS (0.289 g, 1.15 mmol). The reaction gave a mixture of bis THP protected compound and **26.1**.



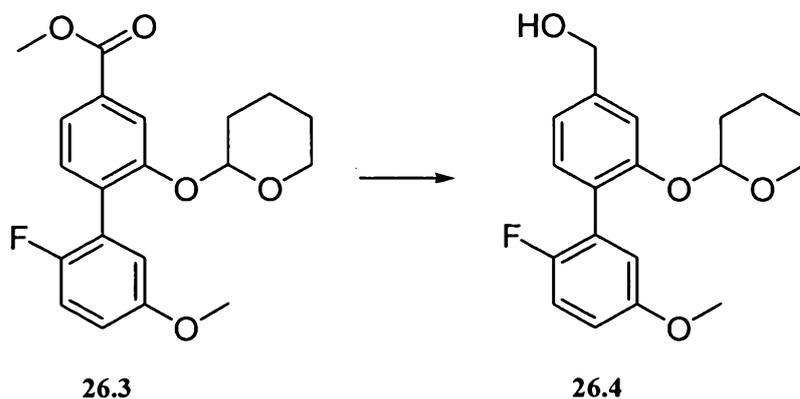
[0362] Methyl 4-bromo-3-(tetrahydro-2H-pyran-2-yloxy)benzoate (26.2).

To flask containing **26.1** (2.15 g, 7.14 mmol) and cesium carbonate (3.95 g, 12.1 mmol) in acetone (50 mL), was added iodomethane (0.667 mL, 10.7 mmol). The resulting mixture was stirred overnight. The reaction was diluted with water and extracted with EtOAc. The organic layers were washed with brine, dried over Na₂SO₄, filtered, concentrated, and then purified by combiflash (0 to 20% EtOAc/ Hexanes) to provide methyl **26.2** (2.25 g, 99% yield).

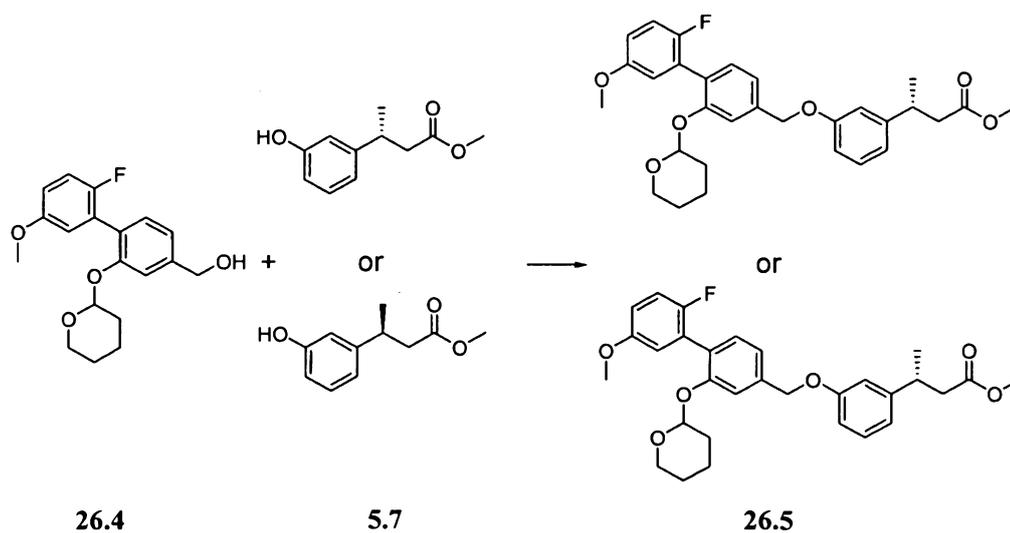


[0363] Methyl 2'-fluoro-5'-(methoxy)-2-(tetrahydro-2H-pyran-2-yloxy)-1,1'-biphenyl-4-carboxylate (26.3).

To a 2 dram vial charged with 2-fluoro-5-methoxyphenylboronic acid (available from Aldrich)(3.17 g, 18.7 mmol), tetrakis(triphenylphosphine)palladium (0) (0.719 g, 0.622 mmol), cesium fluoride (1.15 mL, 31.1 mmol), and **26.2** (1.96 g, 6.22 mmol), was added DME (20 mL). The reaction mixture was then heated at 90 °C overnight. The reaction was allowed to cool and then filtered and concentrated. The crude product was purified by combiflash (0 to 10% EtOAc/hexanes) yielding **26.3** (1.61 g, 71.8% yield).

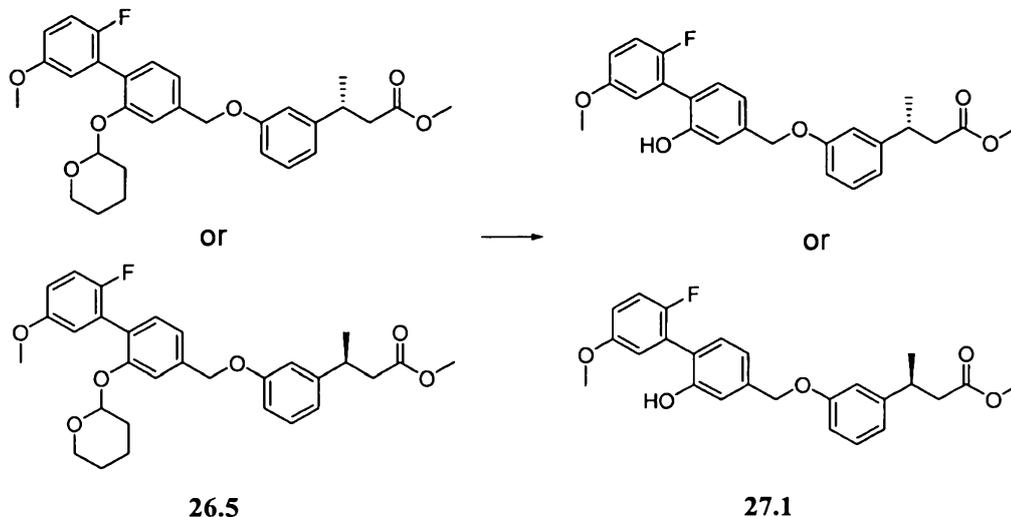


[0364] **(2'-Fluoro-5'-(methoxy)-2-(tetrahydro-2H-pyran-2-yloxy)-1,1'-biphenyl-4-yl)methanol (26.4)**. To **26.3** (1.61 g, 4.47 mmol) in THF (10 mL) at 0 °C, was added LAH (1.0M solution in THF, 6.70 mL, 6.70 mmol). The reaction was stirred for one hour and then carefully diluted with water, extracted with EtOAc, washed with brine, dried over sodium sulfate, filtered, and concentrated to provide **26.4** (0.990 g, 66.7% yield).



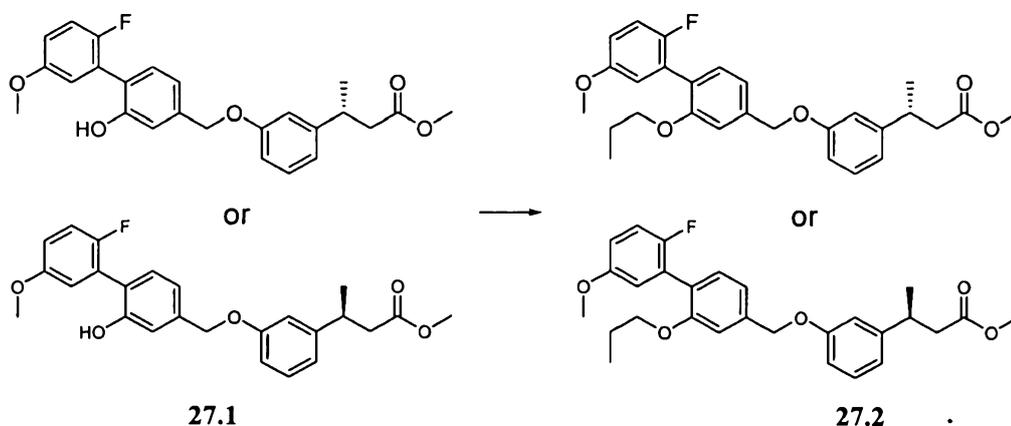
[0365] **Methyl (3R)-3-(3-(((2'-fluoro-5'-(methoxy)-2-(tetrahydro-2H-pyran-2-yloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate or methyl (3S)-3-(3-(((2'-fluoro-5'-(methoxy)-2-(tetrahydro-2H-pyran-2-yloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate (26.5)**. To a flask containing **5.7** (150.0 mg, 772.3 μ mol), **26.4** (308.0 mg, 926.8 μ mol), and polymer supported triphenylphosphine (386.1 mg, 1158 μ mol) in DCM (3 mL) was added diethyl azodicarboxylate (182.4 μ L, 1158 μ mol) at 0 °C. The reaction mixture was allowed to warm to room temperature and

[0367]

Example 27

[0368]

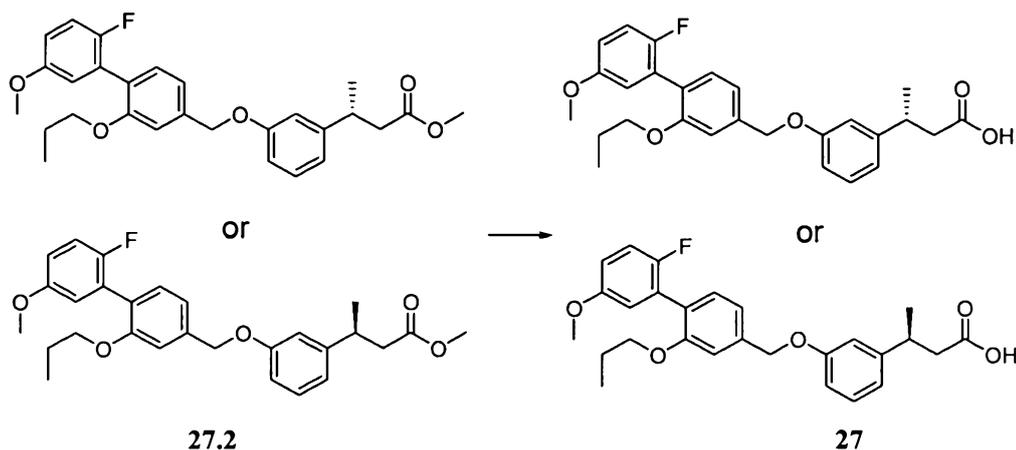
Methyl (3R)-3-(3-(((2'-fluoro-2-hydroxy-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate or methyl (3S)-3-(3-(((2'-fluoro-2-hydroxy-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate (27). To a solution of 26.5 (250 mg, 492 μ mol) in MeOH (2.5 mL), was added PPTS (12.4 mg, 49.2 μ mol) at room temperature. The mixture was heated overnight, cooled to room temperature, diluted with EtOAc, washed with water and brine, dried (MgSO_4), and concentrated. The crude product was purified by silica gel flash chromatography (0-25% EtOAc/hexane) to afford 27.1 (179.1 mg, 85.8% yield) as a colorless oil.



[0369]

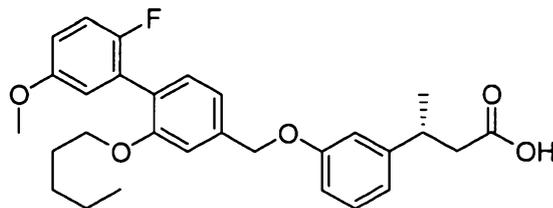
Methyl (3R)-3-(3-(((2'-fluoro-5'-(methoxy)-2-(propoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate or methyl (3S)-3-(3-(((2'-fluoro-5'-(methoxy)-2-(propoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate (27.2).

To a flask containing **27.1** (15.0 mg, 35.3 μmol) and cesium carbonate (23.0 mg, 70.7 μmol) in DMF (1 mL), was added 1-bromopropane (5.78 μL , 63.6 μmol), and the resulting mixture was stirred overnight. The reaction was diluted with water and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 , filtered, concentrated, and then purified by combiflash (0 to 20% EtOAc/ Hexanes) to provide **27.2**.

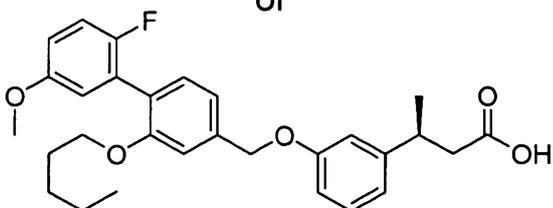


[0370] **(3R)-3-(3-(((2'-Fluoro-5'-(methoxy)-2-(propoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2'-fluoro-5'-(methoxy)-2-(propoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (27)**. To a solution of **27.2** (16.5 mg, 35.3 μmol) in THF/MeOH (2/1) (1.5 mL) was added lithium hydroxide (0.500 mL, 500 μmol). The resulting mixture was stirred overnight at 23 $^{\circ}\text{C}$, quenched with excess 1N HCl, and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude residue was purified by combiflash (5 to 25% EtOAc/hexanes) to afford a **27** (12.5 mg, 78.3% yield). ESI (neg.) m/e: 451.1 (M-H)⁻.

[0371]

Example 28

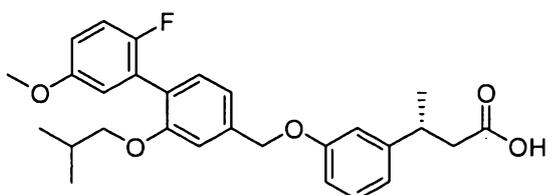
OR



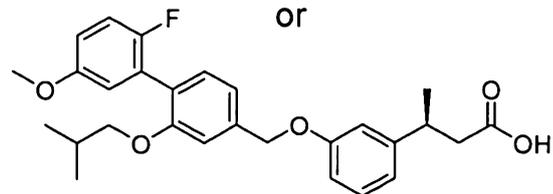
28

[0372] (3R)-3-(3-(((2'-Fluoro-5'-(methoxy)-2-(pentyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2'-fluoro-5'-(methoxy)-2-(pentyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (28). Compound 28 was synthesized from 27.1 by a method analogous to that used to prepare compound 27. ESI (neg.) m/e: 479.2 (M-H)⁺.

[0373]

Example 29

OR

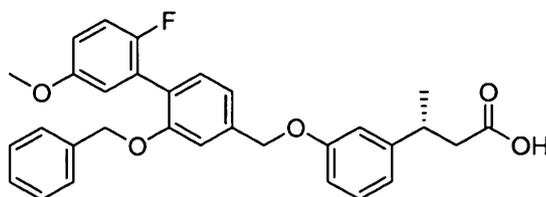


29

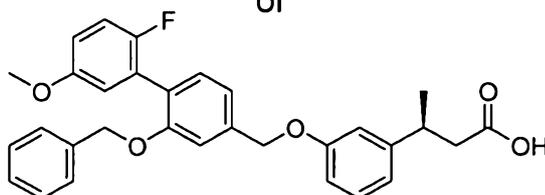
[0374] (3R)-3-(3-(((2'-Fluoro-5'-(methoxy)-2-((2-methylpropyl)oxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2'-fluoro-5'-(methoxy)-2-((2-methylpropyl)oxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic

acid (29). Compound 29 was synthesized from 27.1 by a method analogous to that used to prepare compound 27. ESI (neg.) m/e: 465.2 (M-H)⁺.

[0375] **Example 30**



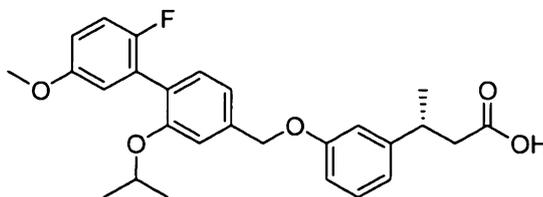
or



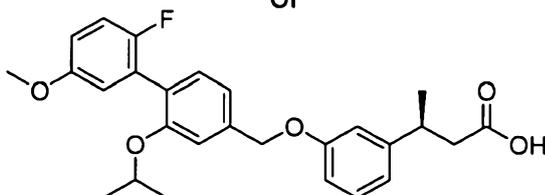
30

[0376] **(3R)-3-(3-(((2'-Fluoro-5'-(methoxy)-2-((phenylmethyl)oxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2'-fluoro-5'-(methoxy)-2-((phenylmethyl)oxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (30).** Compound 30 was synthesized from 27.1 using a method analogous to that used to prepare compound 27. ESI (neg.) m/e: 499.1 (M-H)⁺.

[0377] **Example 31**



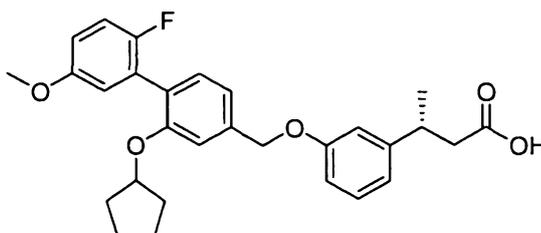
or



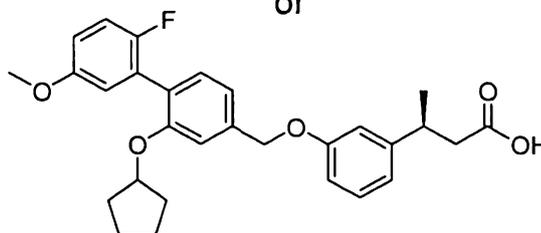
31

[0378] **(3R)-3-(3-(((2'-Fluoro-2-((1-methylethyl)oxy)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2'-fluoro-2-((1-methylethyl)oxy)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (31).** Example 31 was synthesized from 27.1 by a method analogous to that used to prepare compound 27. ESI (neg.) m/e: 451.1 (M-H)⁺.

[0379] **Example 32**



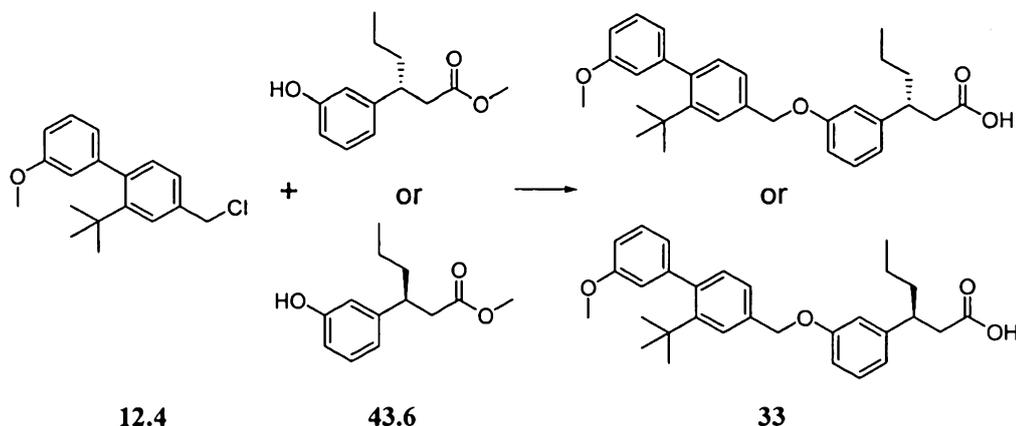
or



32

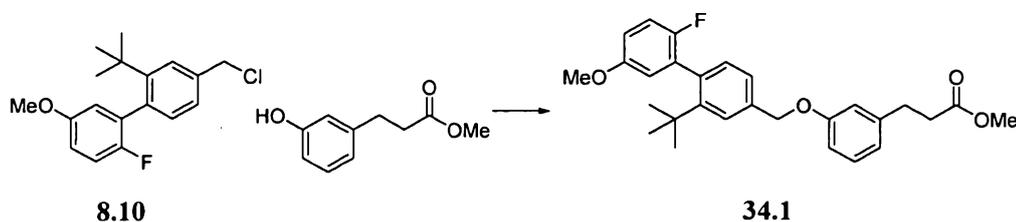
[0380] **(3R)-3-(3-(((2-(Cyclopentyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(cyclopentyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (32).** Example 32 was synthesized from 27.1 by a method analogous to that used to prepare compound 27. ESI (neg.) m/e: 477.2 (M-H)⁺.

[0381]

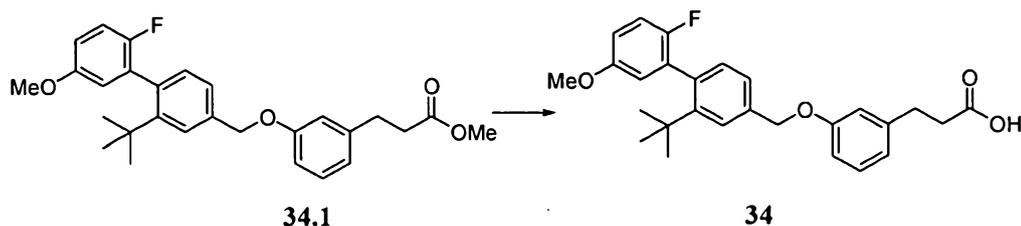
Example 33

[0382] **(3R)-3-(3-(((2-(1,1-Dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (33).** Compound 43.6 (0.015 g, 0.067 mmol) was coupled with 12.4 (0.021 g, 0.074 mmol) according to the method described for preparation of 42 to afford 33 (0.025 g, 81%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.57 (d, 1H), 7.24 (m, 3H), 7.05 (d, 1H), 6.87 (m, 4H), 6.82 (m, 2H), 5.06 (s, 2H), 3.81 (s, 3H), 3.08 (m, 1H), 2.63 (m, 2H), 1.61 (m, 2H), 1.22 (s, 9H), 1.19 (m, 2H), 0.86 (t, 3H).

[0383]

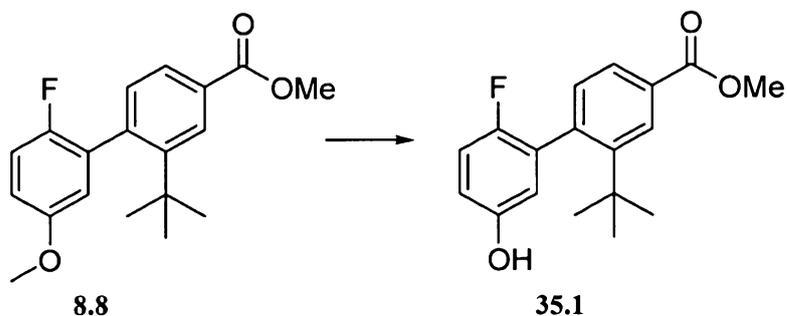
Example 34

[0384] **Methyl 3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (34.1).** Methyl 3-(3-hydroxyphenyl)propanoate (commercially available from Agile Labs Division of Tyger Scientific)(0.025 g, 0.14 mmol) was alkylated by reaction with compound 8.10 (0.043 g, 0.14 mmol) according to the method given in Example 1 to give compound 34.1 as a clear oil (0.052 g, 83% yield). MS ESI (pos.) m/e: 473.2 (M+Na)⁺, 468.2 (M+H₂O)⁺.

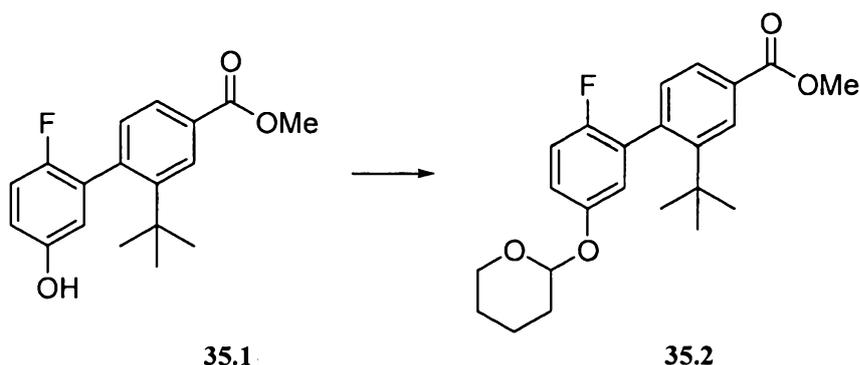


[0385] **3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methoxy)phenyl)propanoic acid (34).** Compound **34.1** (0.052 g, 0.12 mmol) was hydrolyzed according to the method reported for Example 1 to give compound **34** as a clear oil (0.0376 g, 75% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.61 (1 H, d, J=1.6 Hz), 7.31 - 7.23 (2 H, m), 7.06 (1 H, d, J= 8.2 Hz), 7.00 (1 H, t, J= 8.6 Hz), 6.91 - 6.83 (4 H, m), 6.78 (1 H, dd, J=5.9, 3.1 Hz), 5.08 (2 H, s), 3.79 (3 H, s), 2.97 (2 H, t, J=7.8 Hz), 2.71 (2 H, t, J=7.8 Hz), 1.24 (9 H, s). MS ESI (neg.) m/e: 871.5 (2M-H)⁺, 543.2 (M-H)⁺.

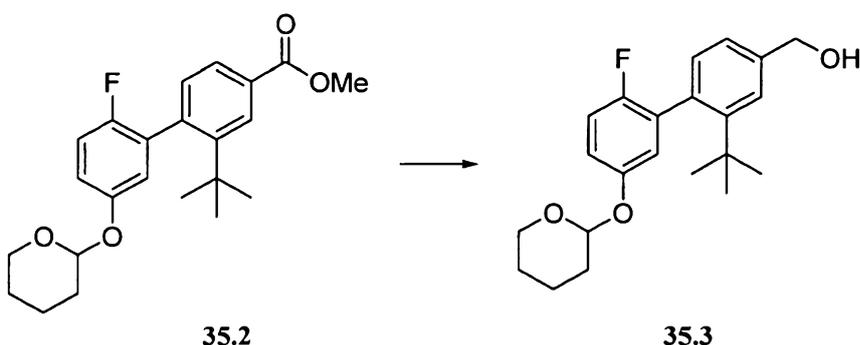
[0386] **Example 35**



[0387] **Methyl 2-(1,1-dimethylethyl)-2'-fluoro-5'-hydroxy-1,1'-biphenyl-4-carboxylate (35.1).** To a cooled solution of **8.8** (0.500 g, 2.00 mmol) in dry DCM (32.0 mL) at 0°C was added boron tribromide (7.00 mL, 7.00 mmol). Stirring was continued for 6 hours, and the reaction was monitored by TLC and LCMS. Upon completion, pH 7 buffer was added to the mixture at 0°C. The resulting solution was extracted with DCM (3 × 20 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-20% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **35.1** as a colorless oil (0.29g, 61%). MS ESI (pos.) m/e: 335.1 (M+Na)⁺, 320.1 (M+H₂O)⁺, 303.1 (M+H)⁺.

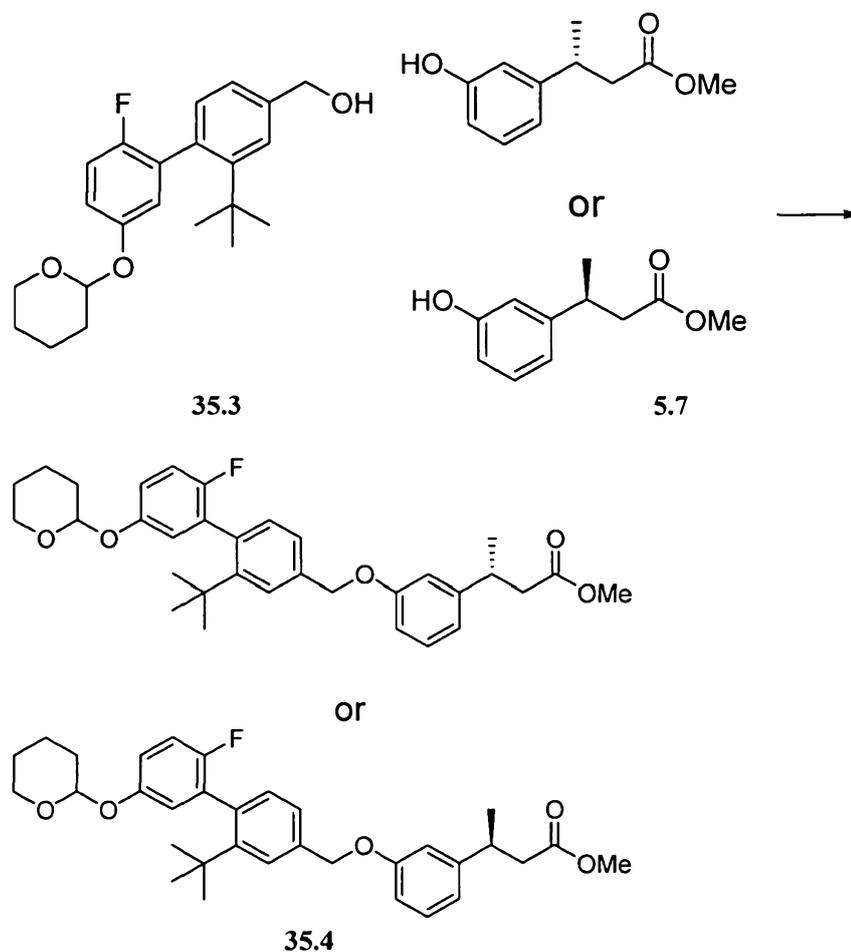


[0388] **Methyl 2-(1,1-dimethylethyl)-2'-fluoro-5'-(tetrahydro-2H-pyran-2-yloxy)-1,1'-biphenyl-4-carboxylate (35.2).** To a stirred solution of **35.1** (0.080 g, 0.30 mmol) in dry DCM (1.00 mL) at 23 °C, was added 3,4-dihydro-2H-pyran (available from Aldrich)(0.04g, 0.50 mmol), followed by PPTS (0.007 g, 0.03 mmol). Stirring was continued for 14 hours. The resulting solution was concentrated in vacuo. Water was added, and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-20% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **35.2** as a colorless oil (0.100 g, 100%). MS ESI (pos.) m/e: 795.4 (2M+Na)⁺.



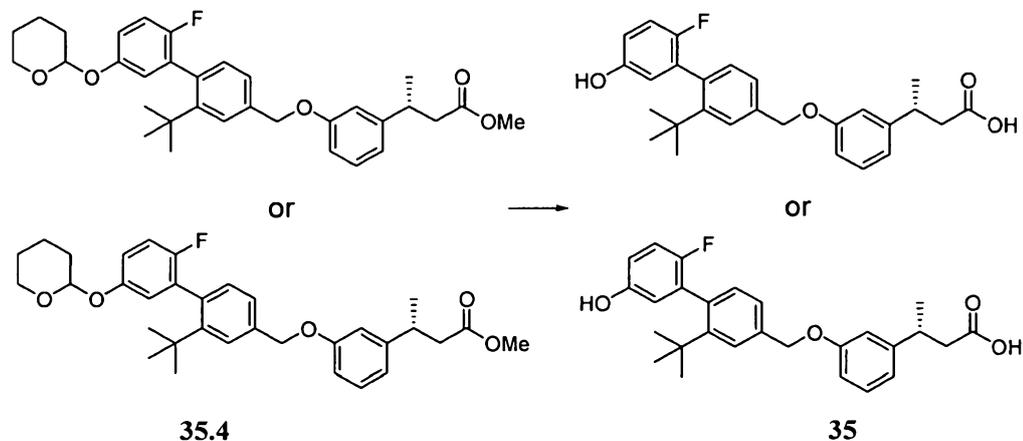
[0389] **(2-(1,1-Dimethylethyl)-2'-fluoro-5'-(tetrahydro-2H-pyran-2-yloxy)-1,1'-biphenyl-4-yl)methanol (35.3).** To a cooled solution of **35.2** (0.080 g, 0.30 mmol) in THF (3.00 mL) at 0°C, was added LAH (1.0 M solution in THF, 0.60 mL, 0.60 mmol). Stirring was continued for 1 hour. 1N NaOH (5 mL) was carefully added to quench the reaction. The resulting solution was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-30% EtOAc in

hexanes). Fractions containing the desired product were combined and concentrated to provide **35.3** as a colorless oil (0.055g, 54%). MS ESI (pos.) m/e: 739.3 (2M+Na)⁺, 376.1 (M+H₂O)⁺.



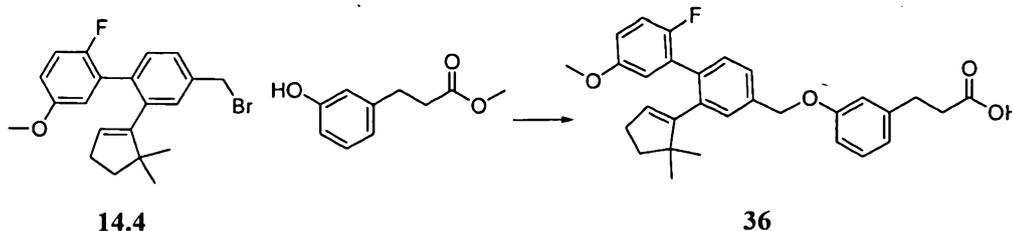
[0390] Methyl (3R)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(tetrahydro-2H-pyran-2-yloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl) butanoate or methyl (3S)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(tetrahydro-2H-pyran-2-yloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl) butanoate (**35.4**). To a stirred solution of compound **5.7** (0.015 g, 0.077 mmol) in THF (0.77 mL) at 0°C, was added **35.3** (0.030 g, 0.085 mmol) and polymer based triphenylphosphine (0.030 g, 0.12 mmol) followed by diethyl azodicarboxylate (0.018 mL, 0.12 mmol). Stirring continued at 23°C for 19 hours. Water (5 mL) was added to quench the reaction, and the resulting solution was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over MgSO₄, filtered and

concentrated in vacuo. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-20% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **35.4** as a colorless oil (0.028g, 68%). MS ESI (pos.) m/e: 557.3 (M+Na)⁺.



[0391] (3R)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-hydroxy-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-hydroxy-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (35). To a stirred solution of compound **35.4** (0.028 g, 0.052 mmol) in THF (2.00 mL) and EtOH (2.00 mL) at 23°C was added a solution of lithium hydroxide (1N, 1.00mL). Stirring was continued for 16 hours. The resulting mixture was concentrated in vacuo. 1 N HCl (5 mL) was added to the solution, and stirring was continued for 24 hours. The mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-40% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide compound **35** as a colorless oil (0.010g, 45%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.60 (1 H, d, J=1.6 Hz), 7.30 - 7.23 (2 H, m), 7.04 (1 H, dd, J=7.8, 1.3Hz), 6.95 (1 H, t, J=8.8Hz), 6.89-6.85 (3H, m), 6.79 (1 H, m), 6.71 (1 H, dd, J=5.9, 3.1 Hz), 5.08 (2 H, s), 3.27 (1 H, m), 2.71 - 2.65 (1 H, dd, J=15.4, 6.6, 2.0 Hz), 2.61 - 2.55 (1 H, dd, J=15.4, 8.1 Hz), 1.33 (3H, d, J=7.0Hz), 1.24 (9 H, s). MS ESI (pos.) m/e: 871.3 (2M-H)⁺, 435.1 (M-H)⁺.

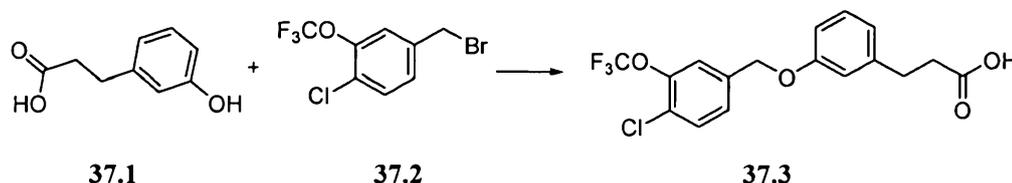
[0392]

Example 36

[0393]

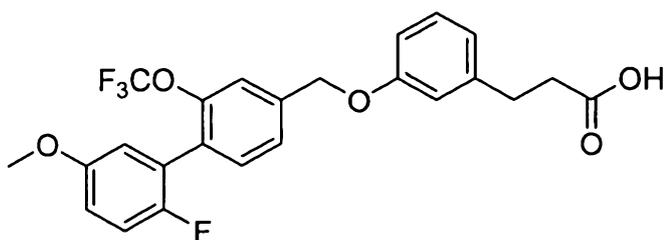
3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (36). A reaction mixture of compound 14.4 (36.0mg, 0.093 mmol), commercially available methyl 3-(3-hydroxyphenyl)propanoate (available from Agile Labs Division of Tyger Scientific)(18.3 mg, 0.093 mmol) and cesium carbonate (60.3 mg, 0.185 mmol) in DMSO (1.0 mL) was stirred at room temperature overnight. LC-MS results indicated the benzylation reaction was completed. MS ESI (pos.) m/e: 511.1 (M+Na)⁺. Lithium hydroxide (18.0 mg, 0.74 mmol, 0.3 mL, 3.33M in water) and DMSO (1. mL) were added. Stirring was continued overnight. 1 N HCl was then added to reach a pH of about 3. The reaction mixture was purified by HPLC (reversed phase) to give the title compound 36. ¹H NMR (400 MHz, CD₃CN) δ ppm 7.44 (dd, 1H), 7.30 - 7.38 (m, 2H), 7.24 (t, 1H), 7.05 (t, 1H), 6.85 - 6.94 (m, 5H), 5.54 (s, 1H), 5.16 (s, 2H), 3.77(s, 3H), 2.89 (t, 2H), 2.62 (t, 2H), 2.22 - 2.31 (m, 2H), 1.66 - 1.71 (m, 2H), 0.87(s, 6H) MS ESI (neg.) m/e: 473.2 (M-H)⁺.

[0394]

Example 37

[0395]

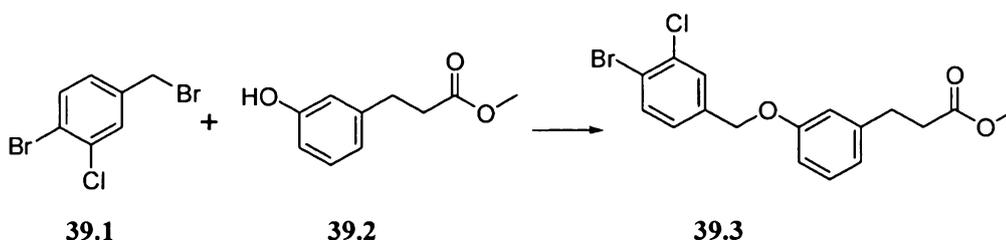
3-(3-(4-Chloro-3-(trifluoromethoxy)benzyloxy)phenyl)-propanoic acid (37.3). Compound 37.3 was synthesized using the alkylation and hydrolysis procedure of Example 13 above using compounds 37.1 and 37.2. 3-(3-Hydroxyphenyl)propanoic acid is available from Alfa Aesar Avocado, and Lancaster). 4-(Bromomethyl)-1-chloro-2-(trifluoromethoxy)benzene is available from Alfa Aesar, Lancaster, and Avocado. MS ESI (neg.) m/e: 373 (M-H).



38

[0398] **3-[3-(2'-Fluoro-5'-methoxy-2-trifluoromethoxy-biphenyl-4-ylmethoxy)-phenyl]-propionic acid (38)**. Compound 38 was synthesized using the procedure described above for preparing 13.3 using compound 37.3 and 2-fluoro-5-methoxyphenylboronic acid 38.1 (available from Aldrich). MS ESI (neg.) m/e: 463 (M-H). ¹H NMR (400 MHz, CD₃CN) δ ppm 7.47 - 7.54 (3 H, m), 7.22 (1 H, t, J=7.8 Hz), 7.12 - 7.17 (1 H, m), 6.98 (1 H, dt, J=9.0, 3.5 Hz), 6.90 - 6.93 (2 H, m), 6.85 (2 H, dd, J=8.0, 2.2 Hz), 5.16 (2 H, s), 3.79 (3 H, s), 2.86 (2 H, s), 2.56 - 2.62 (2 H, m).

[0399] **Example 39**

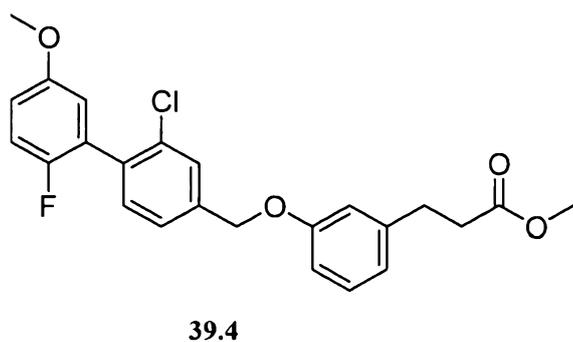
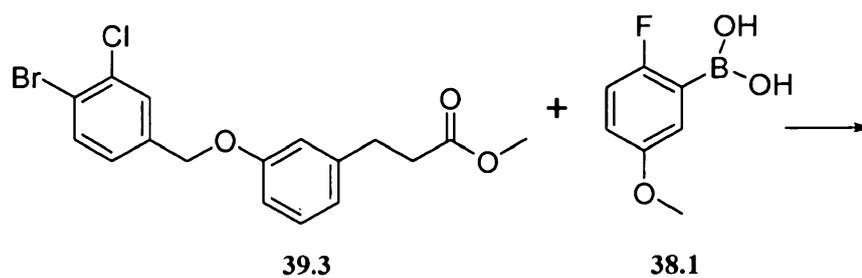


39.1

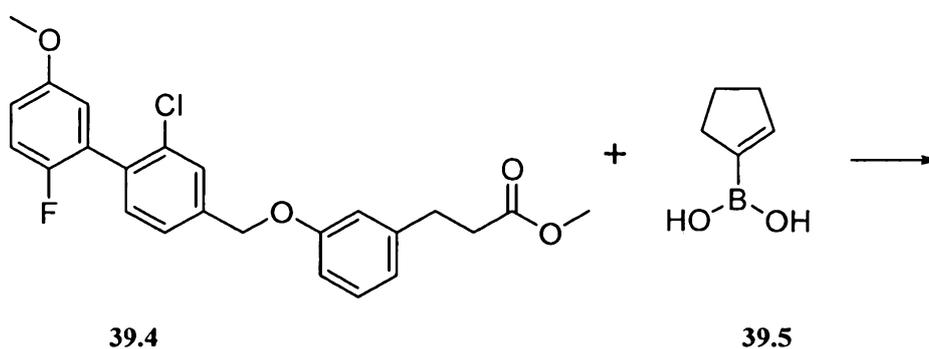
39.2

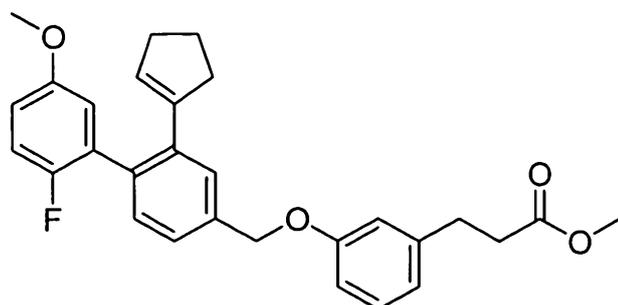
39.3

[0400] **Methyl 3-(3-(4-bromo-3-chlorobenzoyloxy)phenyl)propanoate (39.3)**. Compound 39.3 was synthesized using the procedure described above for preparing 1.1 using 1-bromo-4-(bromomethyl)-2-chlorobenzene 39.1 (available from Metina AB) and methyl 3-(3-hydroxyphenyl)propanoate 39.2 (available from Aagile Labs Division of Tyger Scientific). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.63 (1 H, d, J=8.2 Hz), 7.55 (1 H, d, J=2.0 Hz), 7.17 - 7.24 (2 H, m), 6.78 - 6.85 (3 H, m), 4.99 (2 H, s), 3.68 (3 H, s), 2.94 (2 H, t, J=7.8 Hz), 2.64 (2 H, t, J=7.8 Hz).



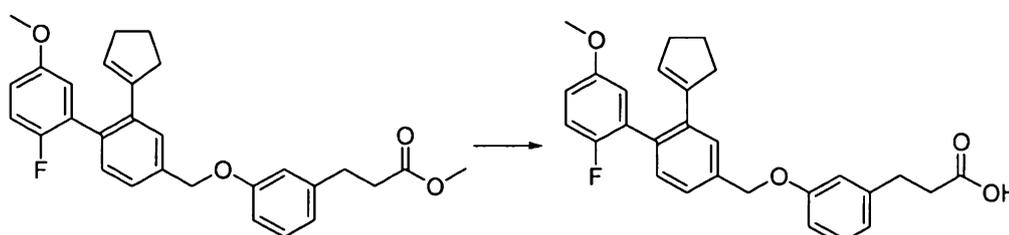
[0401] 3-[3-(2-Chloro-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy)-phenyl]-propionic acid methyl ester (39.4). Compound 39.4 was synthesized using the procedure described above for preparing 13.2 using compound 39.3 and 38.1. MS ESI (pos.) m/e: 451 (M+Na).





39.6

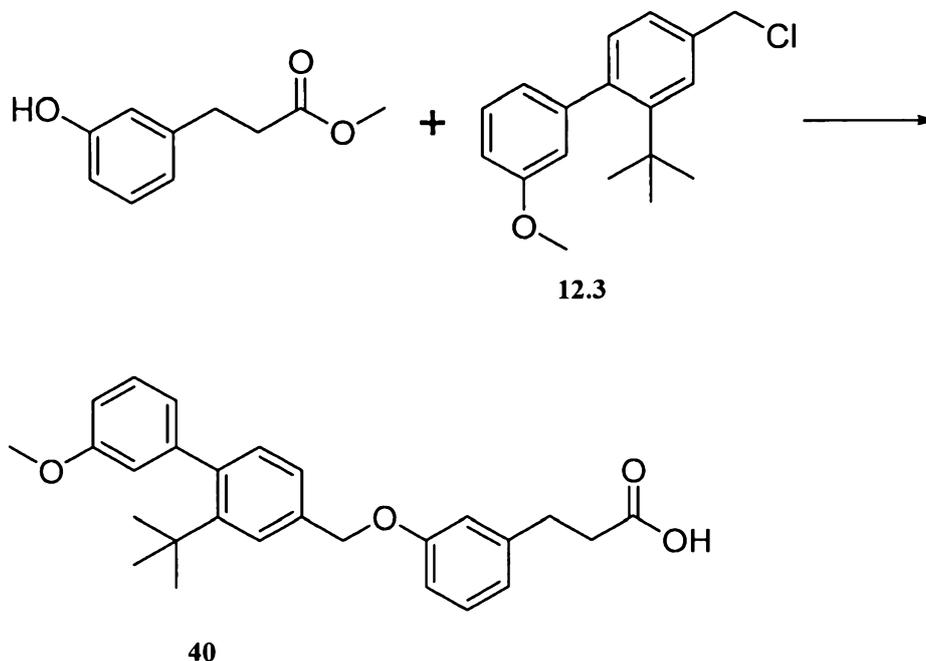
[0402] **3-[3-(2-Cyclopent-1-enyl-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy)-phenyl]-propionic acid methyl ester (39.6).** Compound 39.6 was synthesized using the procedure described above for preparing 13.3 using compound 39.4 and 39.5. MS ESI (pos.) m/e: 483 (M+Na).



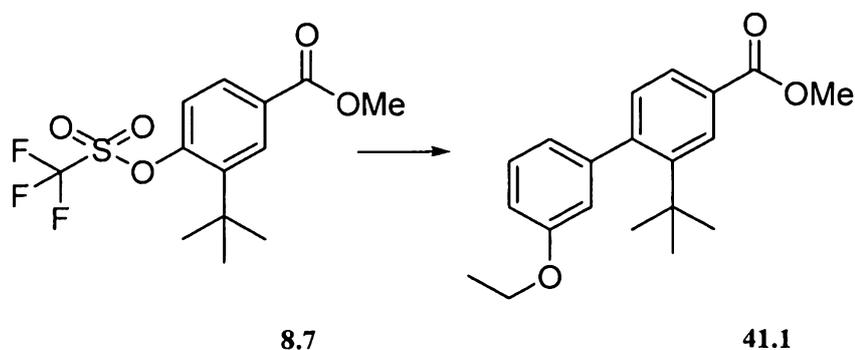
39.6

39

[0403] **3-[3-(2-Cyclopent-1-enyl-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy)-phenyl]-propionic acid (39).** Compound 39 was synthesized using the procedure described above for preparing Example 1 using compound 39.6. MS ESI (neg.) m/e: 445 (M-H). ¹H NMR (400 MHz, CD₃CN) δ ppm 7.45 (1 H, s), 7.37 (1 H, dd, J=7.8, 2.0 Hz), 7.27 (1 H, d, J=7.8 Hz), 7.18 - 7.23 (1 H, m), 7.03 (1 H, t, J=9.2 Hz), 6.82 - 6.90 (4 H, m), 6.82 (1 H, d, J=3.5 Hz), 5.46 (1 H, t, J=2.2 Hz), 5.10 (2 H, s), 3.75 (3 H, s), 2.85 (2 H, t, J=7.6 Hz), 2.58 (2 H, t, J=7.8 Hz), 2.34 - 2.38 (2 H, m), 2.34 (1 H, d, J=2.0 Hz), 2.27 (2 H, ddd, J=9.9, 5.0, 2.3 Hz), 1.76 - 1.84 (2 H, m).

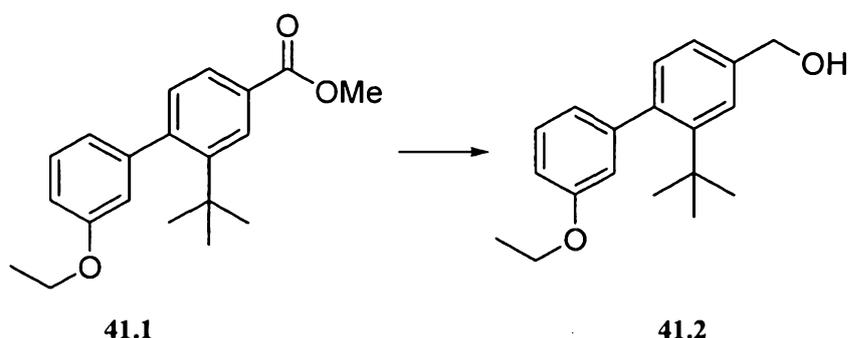
Example 40

[0404] 3-(3-(((2-(1,1-Dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (**40**). Compound **40** was prepared from commercially available methyl 3-(3-hydroxyphenyl)propanoate (available from Agile Labs Division of Tyger Scientific) and **12.3** by a method based on that reported in US 2006/0004012. (MS ESI (neg.) m/e: 417.1 (M-H). ¹H NMR (400 MHz) (CDCl₃) δ ppm 7.59 (1 H, d, J=1.6 Hz), 7.29 (3 H, m), 7.07 (1 H, d, J=7.8 Hz), 6.92 (6 H, m), 5.08 (2 H, s), 3.83 (3 H, s), 2.98 (2 H, t, J=7.8 Hz), 2.75 (2 H, m), 1.24 (9 H, s).

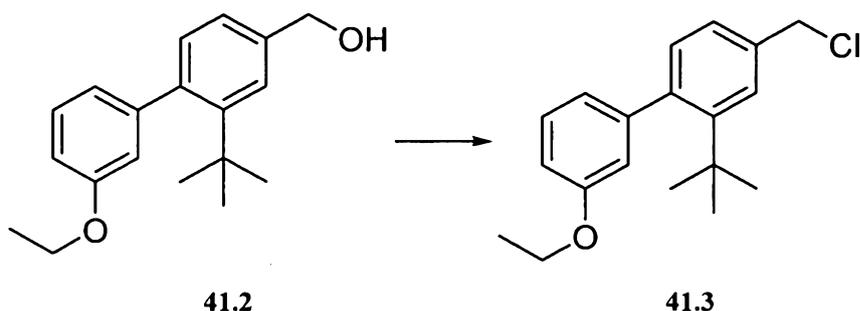
[0405] **Example 41**

[0406] Methyl 2-(1,1-dimethylethyl)-3'-(ethoxy)-1,1'-biphenyl-4-carboxylate (**41.1**). A dry round bottom flask containing **8.7** (1.13 g, 3.31 mmol), 3-

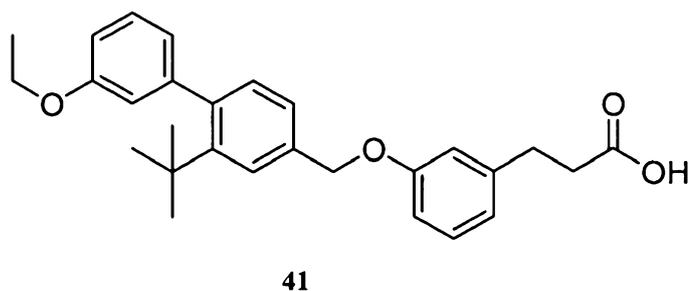
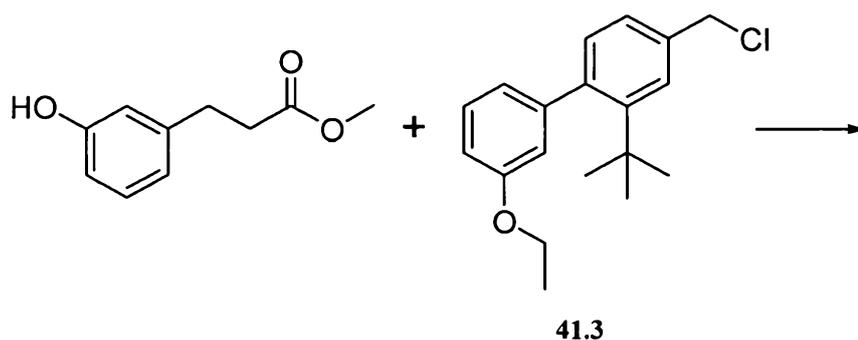
ethoxyphenylboronic acid (available from Aldrich)(1.10 g, 6.63 mmol), tetrakis(triphenylphosphine)palladium (0.39 g, 0.340 mmol), and potassium carbonate (1.41 g, 10.20 mmol) was evacuated and backfilled three times with argon. Dry DMF (10.000 mL) was then added via syringe under argon. The mixture was then heated at 80 °C and monitored with TLC. After 20 hours, the reaction was cooled to room temperature and diluted with water. The mixture was extracted three times with EtOAc and then concentrated under reduced pressure. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-25% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **41.1** as a colorless oil (0.87, 84%). MS ESI (pos.) m/e: 313.1 (M+H)⁺.



[0407] **(2-(1,1-Dimethylethyl)-3'-(ethoxy)-1,1'-biphenyl-4-yl)methanol (41.2)**. To a cooled solution of **41.1** (0.87g, 2.79 mmol) in dry THF (10.0 mL) at 0°C, was added LAH (1.0 M solution in THF (5.5 mL, 5.5 mmol)). Upon complete addition, the reaction was allowed to warm to room temperature and monitored by TLC and LCMS. Upon completion, 1N NaOH (5 mL) was carefully added to quench the reaction. The resulting solution was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-40% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **41.2** as a colorless oil (0.72, 91%). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.53 (1 H, d, J= 1.5 Hz), 7.26 (1 H, m), 7.19 (1 H, dd, J= 7.7, 1.8 Hz), 7.04 (1 H, d, J=7.6 Hz), 6.89 (3H, m), 4.74 (2 H, d, J= 3.2 Hz), 4.08 (2H, m), 1.71 (1H, s), 1.42 (3H, t, J= 7.0 Hz), 1.23 (9 H, s).

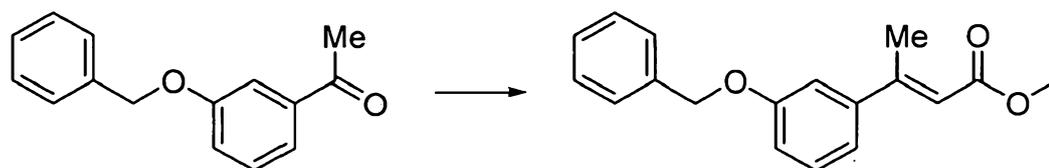


[0408] **4-(Chloromethyl)-2-(1,1-dimethylethyl)-3'-(ethoxy)-1,1'-biphenyl (41.3).** A dry, round bottom flask containing **41.2** (0.72 g, 2.53 mmol) and DCM (9.0 mL) was cooled to 0°C. After 15 minutes, thionyl chloride (1.0 mL, 13.7 mmol) was carefully added dropwise at 0°C. Upon complete addition of thionyl chloride, the mixture was allowed to warm to room temperature and stirred overnight. After 20 hours, the reaction was concentrated under reduced pressure. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-15% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **41.3** as a colorless oil (0.57, 74%). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.54 (1 H, d, J= 2.0 Hz), 7.25 (2H, m), 7.04 (1 H, d, J= 7.4 Hz), 6.90 (3H, m), 4.65 (2 H, s), 4.05 (2H, m), 1.43 (3H, t, J= 7.0 Hz), 1.24 (9H, s).



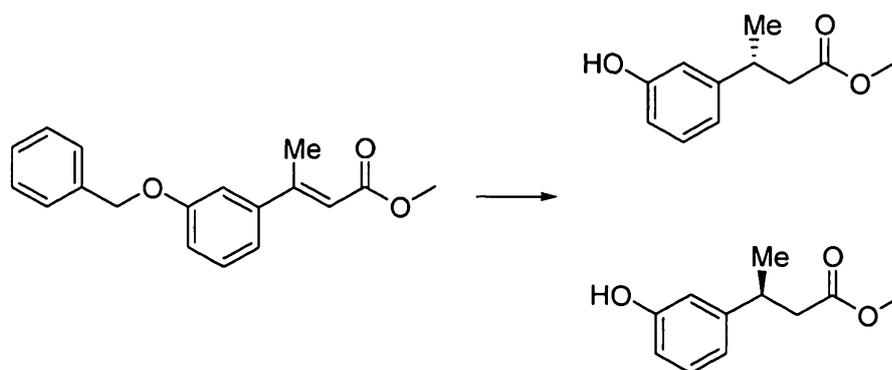
[0409] **3-(3-(((2-(1,1-Dimethylethyl)-3'-(ethoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (41).** Compound 41 was prepared from commercially available methyl 3-(3-hydroxyphenyl)propanoate (available from Aagile Labs Division of Tyger Scientific) and 41.3 by a method based on that reported in US 2006/0004012. (MS ESI (neg.) m/e: 431.2 (M-H). ¹H NMR (400 MHz) (CDCl₃) δ ppm 7.62 (1 H, d, J=1.6 Hz), 7.32 (3 H, m), 7.09 (1 H, d, J=7.8 Hz), 6.95 (5 H, m), 6.87 (1 H, s), 5.10 (2 H, s), 4.07 (2 H, dd, J=6.5, 4.5 Hz), 3.00 (2 H, t, J=7.8 Hz), 2.74 (2 H, t, J=7.8 Hz), 1.45 (3 H, t, J=6.8 Hz), 1.30 (9 H, s).

[0410] **Example 42**



42.1

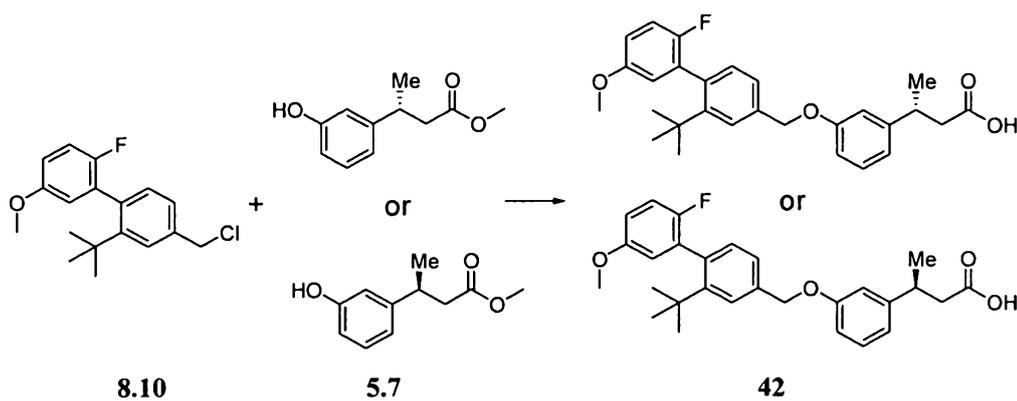
[0411] **Methyl (2E)-3-(3-(benzylmethoxy)phenyl)-2-butenoate (42.1).** To a suspension of lithium chloride (0.28 g, 6.6 mmol) in MeCN (9 mL), were added trimethyl phosphonoacetate (available from Aldrich)(0.76 mL, 5.3 mmol), DBU (0.79 mL, 5.3 mmol), and 3-benzylxyacetophenone (available from Aldrich)(1.00 g, 4.4 mmol). The mixture was stirred overnight at reflux (100 °C), cooled to room temperature, diluted with EtOAc, washed with water and brine, dried (MgSO₄), and concentrated. The crude product was chromatographed on silica gel (0-10% EtOAc/hexane) to afford 42.1 (0.45 g, 36%) as a colorless oil.



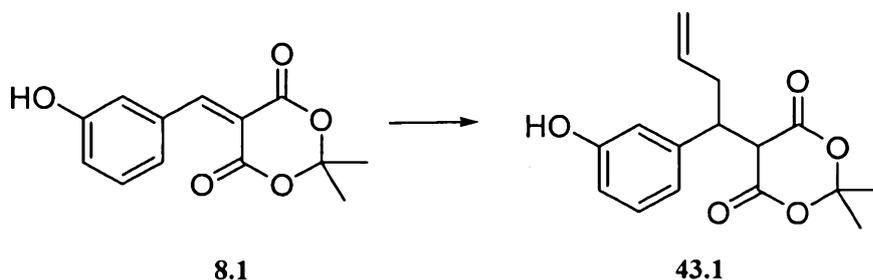
42.1

5.7 and 5.8

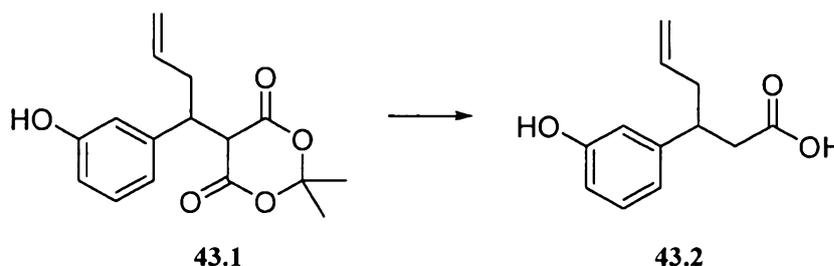
[0412] **Methyl (3R)-3-(3-hydroxyphenyl)butanoate (5.7) and methyl (3S)-3-(3-hydroxyphenyl)butanoate (5.8).** To a solution of **42.1** (0.44 g, 1.56 mmol) in 1:1 EtOAc/MeOH (10.0 mL) was added 10% Pd/C (0.25 g, 0.23 mmol) under a blanket of N₂. The mixture was sparged with H₂, stirred overnight under a H₂ balloon, filtered through silica gel (EtOAc), and concentrated. The resulting racemate was resolved by chiral HPLC (Chiralcel OD column, 3% IPA/hexane, 220 nm) to afford **5.7** (0.14 g, 22.7 minutes) and **5.8** (0.14 g, 36.1 minutes) as pale yellow oils.



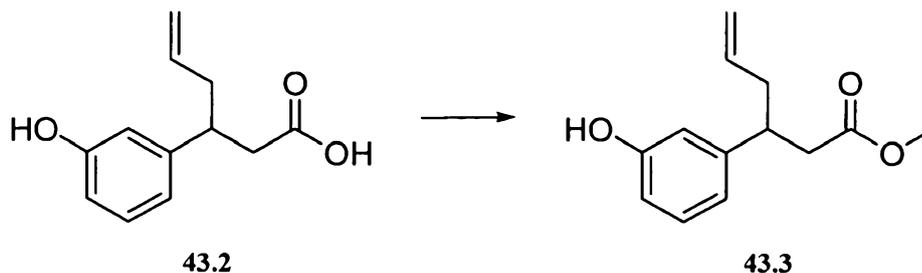
[0413] **(3R)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (42).** A screw-cap vial was charged with **5.7** (0.010 g, 0.051 mmol), **8.10** (0.017 g, 0.057 mmol), cesium carbonate (0.025 g, 0.077 mmol), and DMF (1.0 mL). The mixture was stirred overnight at room temperature, diluted with water, and extracted with EtOAc. The combined organic layers were dried (MgSO₄) and concentrated, and the residue was chromatographed on silica gel (0-15% EtOAc/hexane) to afford a colorless oil. The oil was dissolved in 2:1 THF/MeOH (1.5 mL), and 1 N LiOH (0.5 mL) was added. The mixture was stirred overnight at room temperature, quenched with 1 N HCl (0.6 mL), and extracted with EtOAc. The combined organics were dried (MgSO₄) and concentrated. The crude product was chromatographed on silica gel (0-30% EtOAc/hexane) to afford **42** (0.019 g, 83%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.60 (d, 1H), 7.29 (dd, 1H), 7.25 (t, 1H), 7.05 (d, 1H), 6.99 (t, 1H), 6.86 (m, 4H), 6.77 (dd, 1H), 5.07 (s, 2H), 3.78 (s, 3H), 3.27 (m, 1H), 2.68 (dd, 1H), 2.58 (dd, 1H), 1.32 (d, 3H), 1.23 (s, 9H).

[0414] Example 43

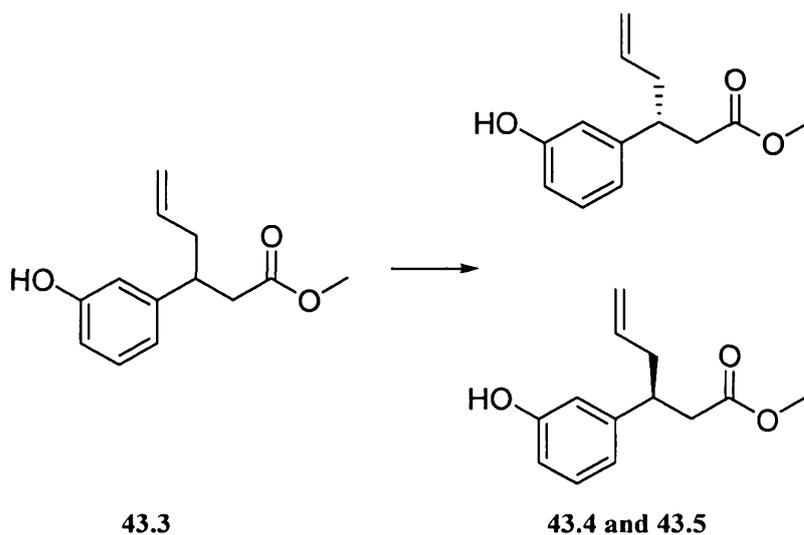
[0415] 5-(1-(3-Hydroxyphenyl)-3-butenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (43.1). To a solution of **8.1** (8.00 g, 32 mmol) in THF (100 mL) was added allylmagnesium chloride (available from Aldrich)(2.0 M in THF) (97 mL, 193 mmol) dropwise at 0°C over 1 hour. When the addition was complete, the reaction was quenched with 1 N HCl and extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO₄), and concentrated. The crude product was chromatographed on silica gel (20-30% EtOAc/hexane) to afford **43.1** (3.4 g, 36%) as a pale yellow oil.



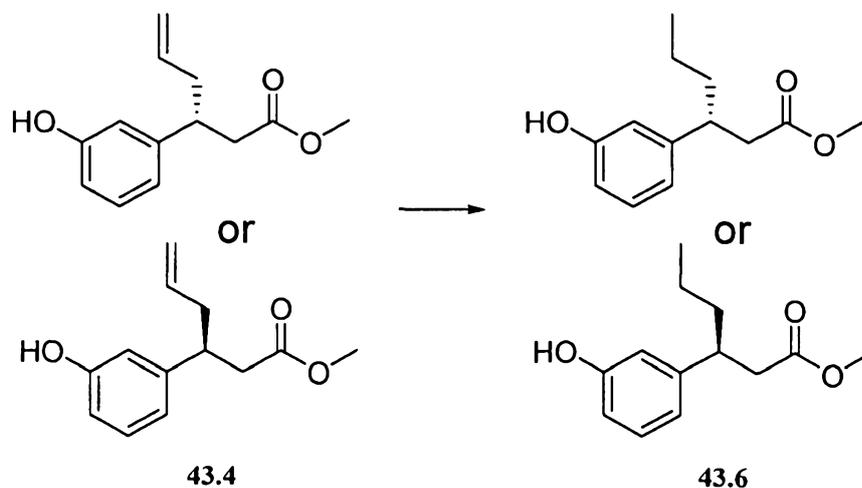
[0416] 3-(3-Hydroxyphenyl)-5-hexenoic acid (43.2). A solution of **43.1** (3.4 g, 12 mmol) in 10:1 DMF/water (48 mL) was stirred overnight at 90 °C. The mixture was cooled to room temperature, diluted with EtOAc, washed with 1 N HCl and brine, dried (MgSO₄), and concentrated to afford **43.2** (2.4 g) as a pink oil. The crude product was used without further purification.



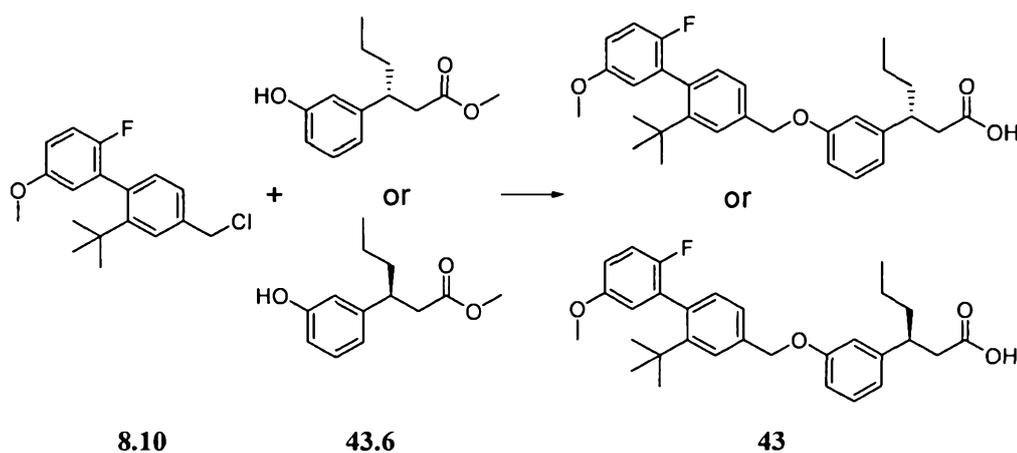
[0417] **Methyl 3-(3-hydroxyphenyl)-5-hexenoate (43.3)**. To a solution of **43.2** (2.4 g, 12 mmol) in MeOH (25 mL) was added five drops of sulfuric acid. The mixture was stirred overnight at reflux, cooled to room temperature, diluted with EtOAc, washed with water and brine, dried (MgSO₄), and concentrated. The crude product was chromatographed on silica gel (0-25% EtOAc/hexane) to afford **43.3** (2.2 g, 84%) as a colorless oil.



[0418] **Methyl (3R)-3-(3-hydroxyphenyl)-5-hexenoate and methyl (3S)-3-(3-hydroxyphenyl)-5-hexenoate (43.4 and 43.5)**. Racemate **43.3** (2.16 g, 9.81 mmol) was resolved by chiral HPLC (Chiralcel OD column, 3% IPA/hexane, 220 nm) to afford **43.4** (1.04 g, 17.8 minutes) and **43.5** (1.00 g, 26.2 minutes) as colorless oils.

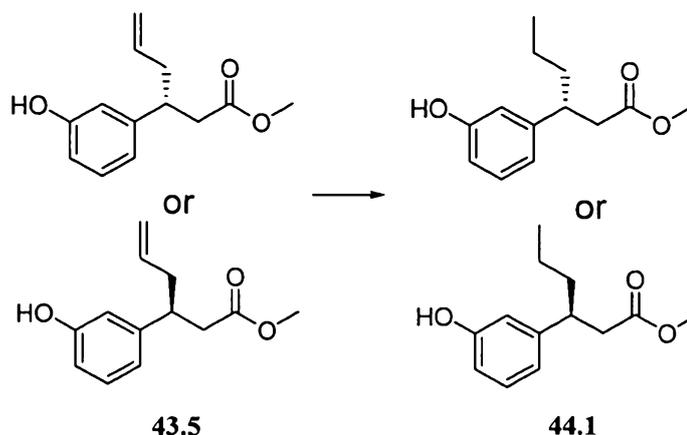


[0419] **Methyl (3R)-3-(3-hydroxyphenyl)hexanoate or methyl (3S)-3-(3-hydroxyphenyl)hexanoate (43.6).** To a solution of **43.4** (0.47 g, 2.1 mmol) in EtOAc (10 mL) was added 10% Pd/C (0.11 g, 0.11 mmol) under a blanket of N₂. The mixture was sparged with H₂, stirred overnight under a H₂ balloon, filtered through silica gel (EtOAc), and concentrated to afford **43.6** (0.47 g, 99%) as a colorless oil.



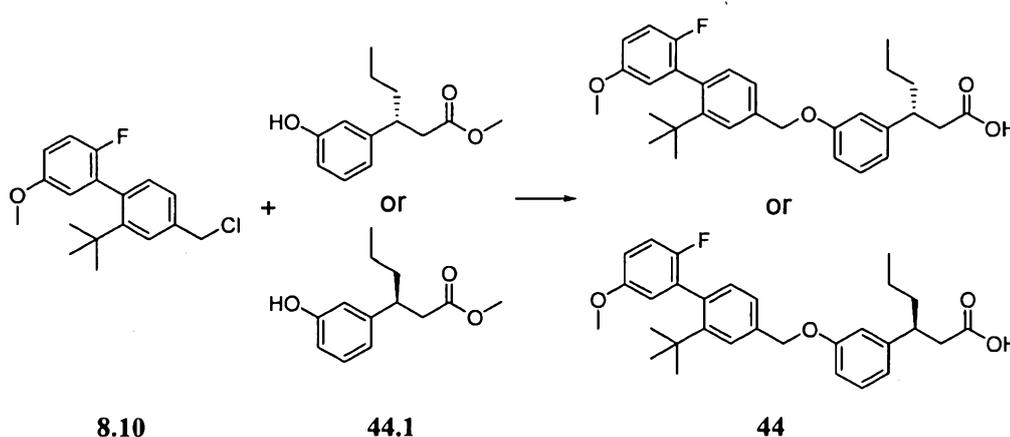
[0420] **(3R)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (43).** Compound **43.6** (0.010 g, 0.045 mmol) was coupled with **8.10** (0.015 g, 0.049 mmol) according to the method described for preparation of **42** to afford **43** (0.018 g, 84%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.60 (d, 1H), 7.29 (dd, 1H), 7.23 (t, 1H), 7.05 (d, 1H), 6.99 (t, 1H), 6.85 (m, 4H), 6.77 (dd, 1H), 5.07 (s, 2H), 3.78 (s, 3H), 3.08 (m, 1H), 2.63 (m, 2H), 1.61 (m, 2H), 1.23 (s, 9H), 1.19 (m, 2H), 0.86 (t, 3H).

[0421]

Example 44

[0422]

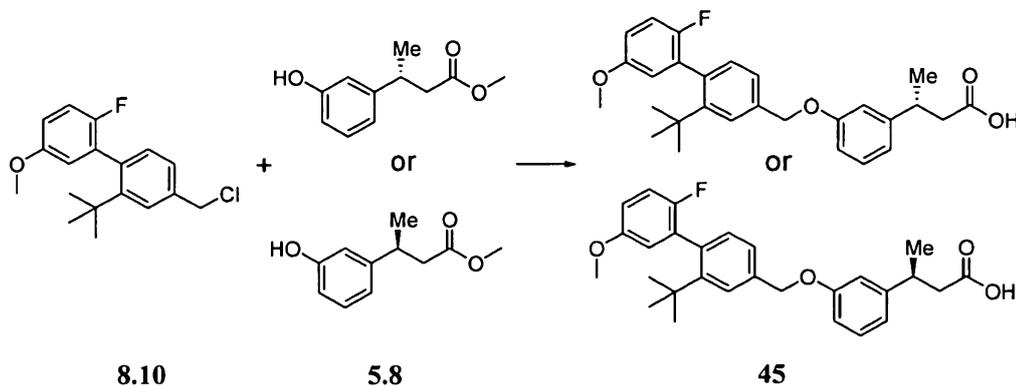
Methyl (3S)-3-(3-hydroxyphenyl)hexanoate or methyl (3R)-3-(3-hydroxyphenyl)hexanoate (44.1). Compound 43.5 (0.47 g, 2.1 mmol) was hydrogenated according to the method described for preparation of 43.6 to afford 44.1 (0.47 g, 99%) as a colorless oil.



[0423]

(3S)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3R)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (44). Compound 44.1 (0.010 g, 0.045 mmol) was coupled with 8.10 (0.015 g, 0.049 mmol) according to the method described for preparation of 42 to afford 44 (0.020 g, 93%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.60 (bs, 1H), 7.29 (d, 1H), 7.23 (t, 1H), 7.05 (d, 1H), 6.99 (t, 1H), 6.84 (m, 4H), 6.77 (dd, 1H), 5.07 (s, 2H), 3.78 (s, 3H), 3.08 (m, 1H), 2.63 (m, 2H), 1.61 (m, 2H), 1.23 (s, 9H), 1.19 (m, 2H), 0.85 (t, 3H).

[0424]

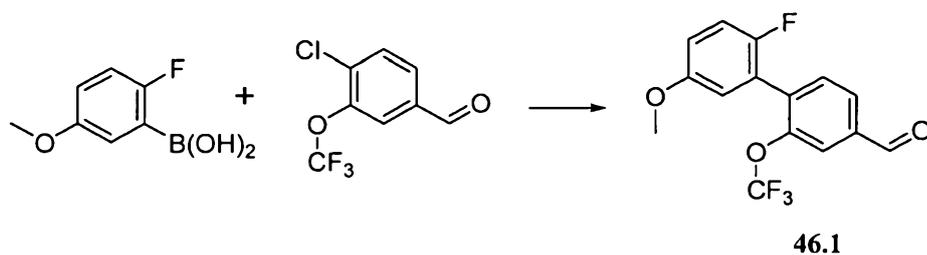
Example 45

[0425]

(3S)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3R)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (45).

Compound 5.8 (0.010 g, 0.051 mmol) was coupled with 8.10 (0.017 g, 0.057 mmol) according to the method described for preparation of 42 to afford 45 (0.022 g, 96%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.60 (d, 1H), 7.29 (dd, 1H), 7.25 (t, 1H), 7.05 (d, 1H), 7.00 (t, 1H), 6.86 (m, 4H), 6.77 (dd, 1H), 5.07 (s, 2H), 3.78 (t, 3H), 3.27 (m, 1H), 2.68 (dd, 1H), 2.58 (dd, 1H), 1.33 (d, 3H), 1.24 (s, 9H).

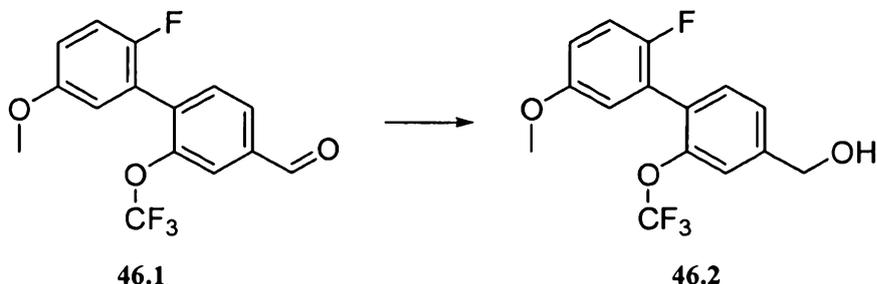
[0426]

Example 46

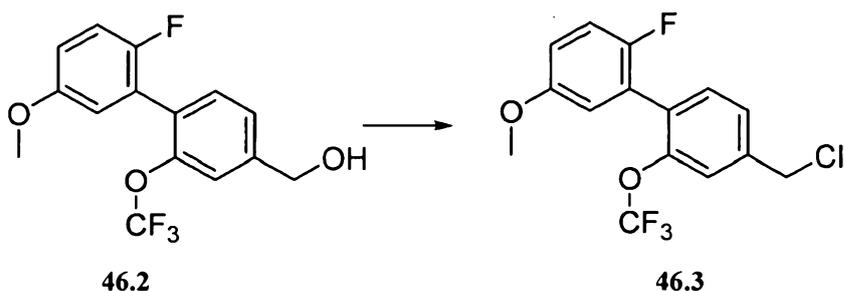
[0427]

2'-Fluoro-5'-(methoxy)-2-((trifluoromethyl)oxy)-1,1'-biphenyl-4-carbaldehyde (46.1). A screw-cap vial was charged with 4-chloro-3-(trifluoromethoxy)benzaldehyde (available from Alfa Aesar, Avocado, Lancaster)(0.184 g, 0.82 mmol), 2-fluoro-5-methoxyphenylboronic acid (available from Aldrich)(0.278 g, 1.64 mmol), potassium phosphate (0.522 g, 2.46 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.101 g, 0.25 mmol), palladium(II) acetate (0.018 g, 0.082 mmol), and 5:1 THF/DMF (3.6 mL). The mixture was stirred overnight at 40 °C, cooled to room temperature, diluted with EtOAc, washed with water and brine, dried (MgSO₄), and

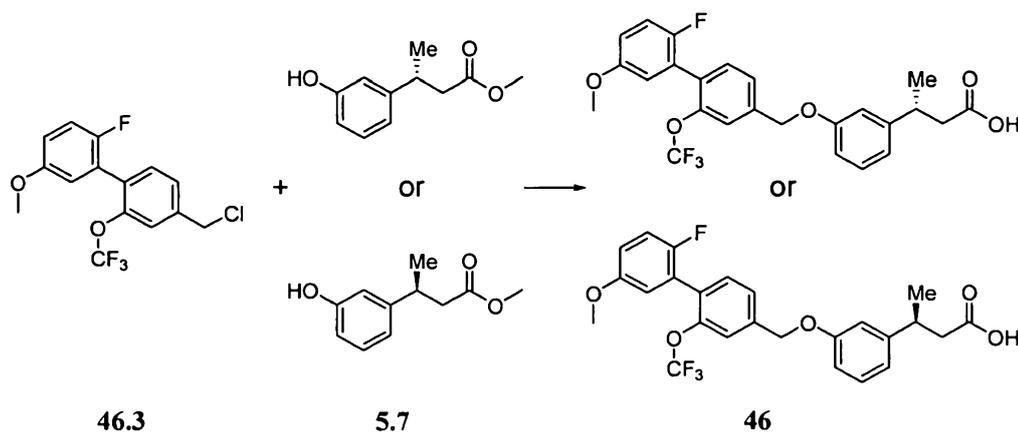
concentrated. The crude product was chromatographed on silica gel (0-10% EtOAc/hexane) to afford **46.1** (165 mg, 64%) as a colorless oil.



[0428] **(2'-Fluoro-5'-(methoxy)-2-((trifluoromethyl)oxy)-1,1'-biphenyl-4-yl)methanol (46.2)**. To a solution of **46.1** (0.165 g, 0.53 mmol) in MeOH (6 mL) was added sodium borohydride (0.040 g, 1.05 mmol) in one portion at room temperature. The mixture was stirred for 30 minutes, quenched with 1 N HCl, and extracted with EtOAc. The combined organic layers were washed with water and brine, dried (MgSO₄), and concentrated. The crude product was chromatographed on silica gel (0-30% EtOAc/hexane) to afford **46.2** (0.164 g, 99%) as a colorless oil.

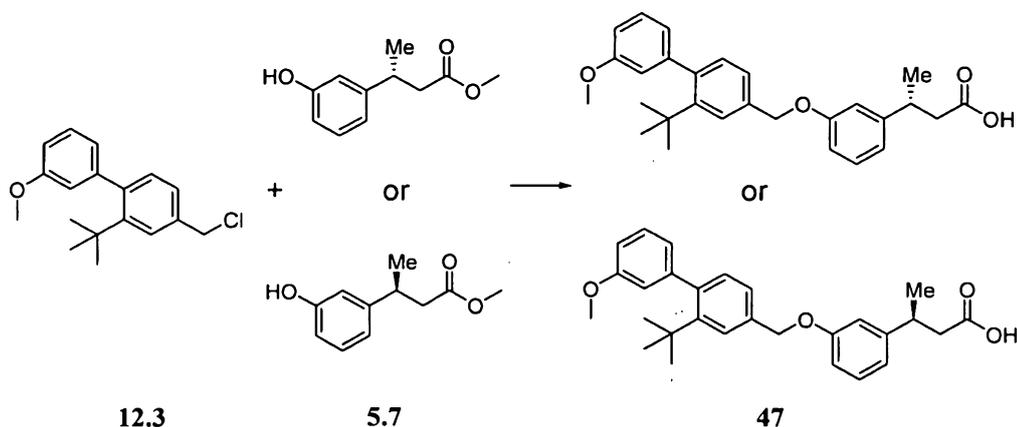


[0429] **4-(Chloromethyl)-2'-fluoro-5'-(methoxy)-2-((trifluoromethyl)oxy)-1,1'-biphenyl (46.3)**. To a solution of **46.2** (0.164 g, 0.52 mmol) in DCM (5 mL) was added thionyl chloride (76 μ L, 1.04 mmol) in one portion at room temperature. The mixture was stirred overnight and concentrated. The crude product was chromatographed on silica gel (0-10% EtOAc/hexane) to afford **46.3** (0.009 g, 5%) as a colorless oil.



[0430] (3R)-3-(3-(((2'-Fluoro-5'-(methoxy)-2-((trifluoromethyl)oxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2'-fluoro-5'-(methoxy)-2-((trifluoromethyl)oxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (**46**). Compound **5.7** (0.006 g, 0.029 mmol) was coupled with **46.3** (0.009 g, 0.026 mmol) according to the method described for preparation of **42** to afford **46** (0.009 g, 69%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.44 (m, 3H), 7.25 (t, 1H), 7.07 (t, 1H), 6.86 (m, 5H), 5.11 (s, 2H), 3.81 (s, 3H), 3.27 (m, 1H), 2.68 (dd, 1H), 2.58 (dd, 1H), 1.32 (d, 3H).

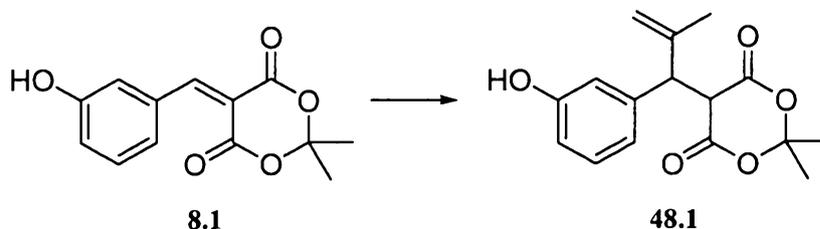
[0431] Example 47



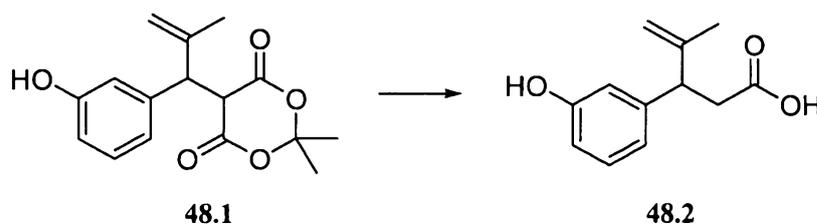
[0432] (3R)-3-(3-(((2-(1,1-Dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (**47**). Compound **5.7** (0.021 g, 0.11 mmol) was coupled with **12.3** (0.034 g, 0.12 mmol) according to the method described for preparation of **42** to afford **47** (0.042 g, 90%) as a colorless oil. ¹H

NMR (400 MHz, CDCl₃) δ ppm 7.58 (d, 1H), 7.25 (t, 3H), 7.06 (d, 1H), 6.87 (m, 6H), 5.07 (s, 2H), 3.81 (s, 3H), 3.27 (m, 1H), 2.69 (dd, 1H), 2.58 (dd, 1H), 1.33 (d, 3H), 1.22 (s, 9H).

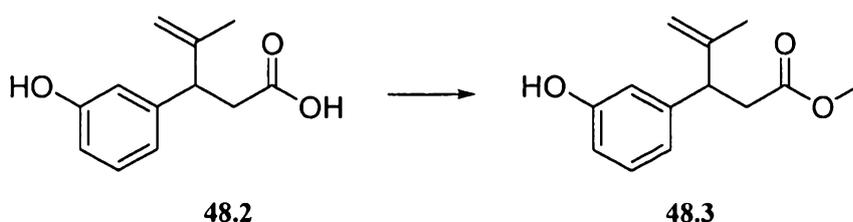
[0433] **Example 48**



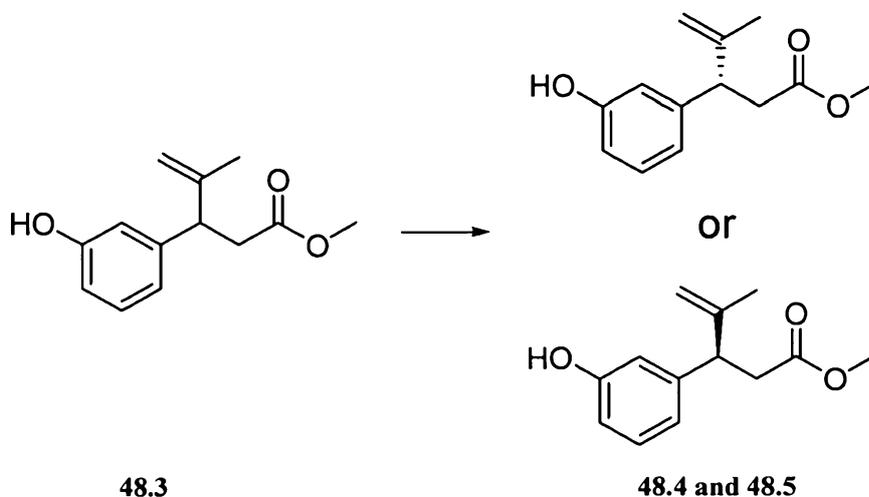
[0434] **5-(1-(3-Hydroxyphenyl)-2-methyl-2-propenyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (48.1).** Compound 8.1 (2.00 g, 8.1 mmol) was treated with isopropenylmagnesium bromide (available from Aldrich)(0.5 M in THF) (97 mL, 48 mmol) according to the method described for preparation of 43.1 to afford 48.1 (0.88 g, 38%) as a yellow oil.



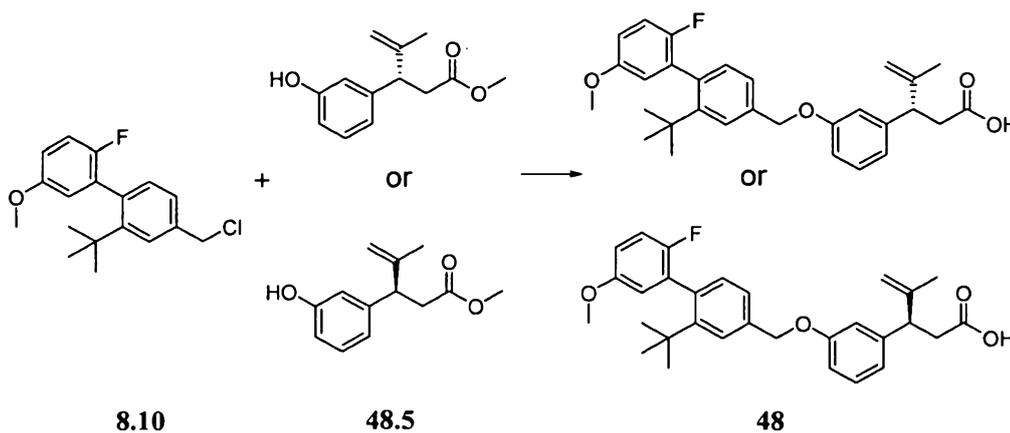
[0435] **3-(3-Hydroxyphenyl)-4-methyl-4-pentenoic acid (48.2).** Compound 48.1 (0.88 g, 3.0 mmol) was hydrolyzed according to the method described for preparation of 43.2 to afford 48.2 (0.63 g).



[0436] **Methyl 3-(3-hydroxyphenyl)-4-methyl-4-pentenoate (48.3).** Compound 48.2 (0.63 g, 3.1 mmol) was esterified according to the method described for preparation of 43.3 to afford 48.3 (0.56 g, 83%) as a colorless oil.



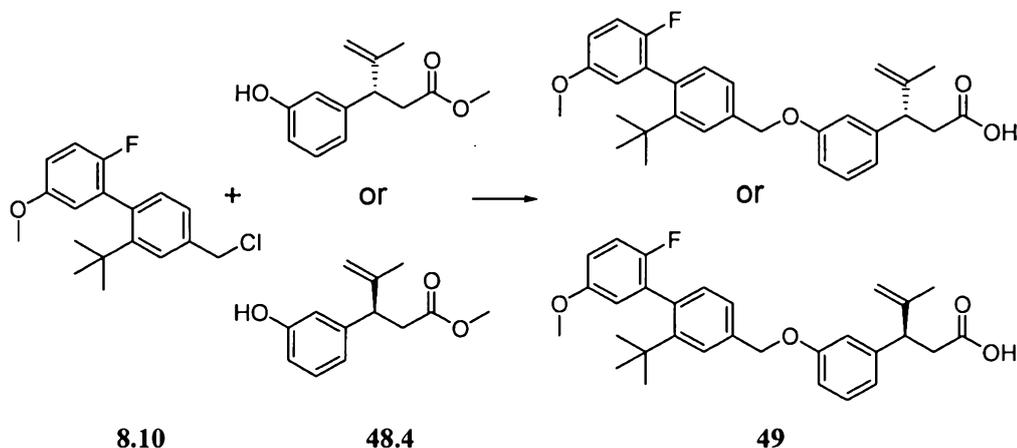
[0437] Methyl (3S)-3-(3-hydroxyphenyl)-4-methyl-4-pentenoate and methyl (3R)-3-(3-hydroxyphenyl)-4-methyl-4-pentenoate (**48.4** and **48.5**). Racemate **48.3** (0.56 g, 2.5 mmol) was resolved by chiral HPLC (Chiralcel OD column, 3% IPA/hexane, 220 nm) to afford **48.4** (0.25 g, 19.0 minutes) and **48.5** (0.26 g, 23.8 minutes) as colorless oils.



[0438] (3R)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-methyl-4-pentenoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-methyl-4-pentenoic acid (**48**). Compound **48.5** (0.015 g, 0.068 mmol) was coupled with **8.10** (0.023 g, 0.075 mmol) according to the method described for preparation of **42** to afford **48** (0.032 g, 99%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.59 (d,

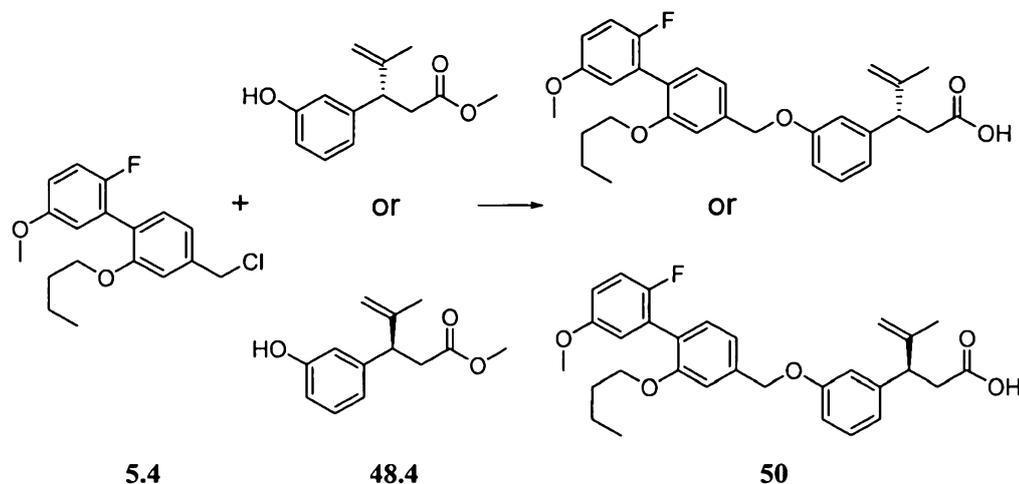
1H), 7.28 (dd, 1H), 7.24 (t, 1H), 7.04 (d, 1H), 6.99 (t, 1H), 6.86 (m, 4H), 6.76 (dd, 1H), 5.07 (s, 2H), 4.93 (s, 1H), 4.90 (bt, 1H), 3.78 (s, 3H), 3.76 (t, 1H), 2.89 (dd, 1H), 2.75 (dd, 1H), 1.62 (s, 3H), 1.23 (s, 9H).

[0439]

Example 49

[0440] **(3S)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-methyl-4-pentenoic acid or (3R)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-methyl-4-pentenoic acid (49).** Compound 48.4 (0.015 g, 0.068 mmol) was coupled with 8.10 (0.023 g, 0.075 mmol) according to the method described for preparation of 42 to afford 49 (0.024 g, 74%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.59 (d, 1H), 7.28 (dd, 1H), 7.24 (t, 1H), 7.04 (d, 1H), 6.99 (t, 1H), 6.86 (m, 4H), 6.76 (dd, 1H), 5.07 (s, 2H), 4.93 (s, 1H), 4.90 (bt, 1H), 3.78 (s, 3H), 3.76 (t, 1H), 2.89 (dd, 1H), 2.75 (dd, 1H), 1.62 (s, 3H), 1.23 (s, 9H).

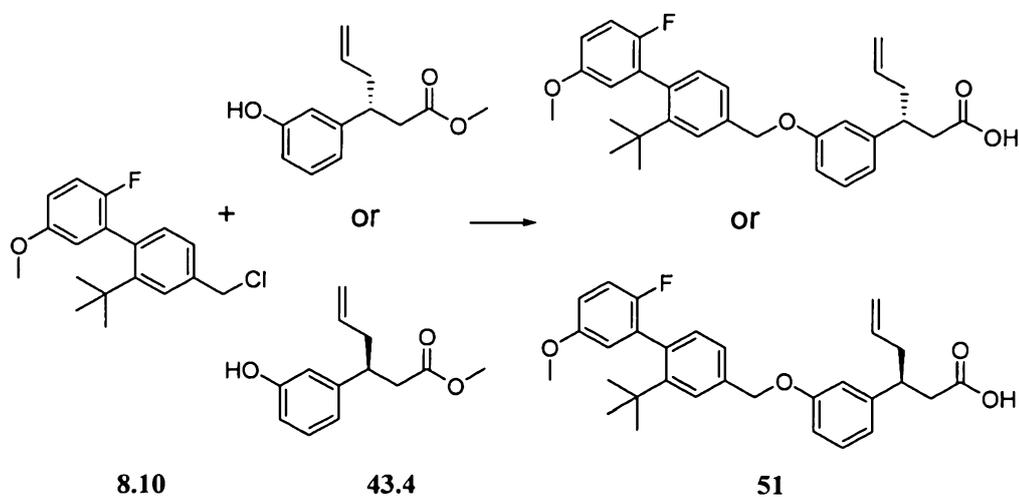
[0441]

Example 50

[0442]

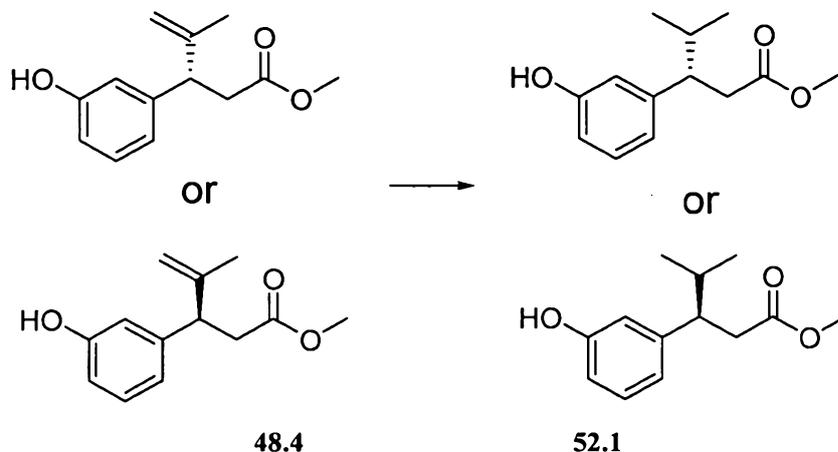
(3S)-3-(3-(((2-(Butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-methyl-4-pentenoic acid or (3R)-3-(3-(((2-(butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-methyl-4-pentenoic acid (50). Compound 48.4 (0.014 g, 0.064 mmol) was coupled with 5.4 (0.023 g, 0.070 mmol) according to the method described for preparation of 42 to afford 50 (0.027 g, 87%) as a colorless oil. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 7.28 (d, 1H), 7.23 (t, 1H), 7.06 (m, 2H), 7.02 (t, 1H), 6.85 (m, 5H), 5.06 (s, 2H), 4.93 (s, 1H), 4.90 (s, 1H), 3.98 (t, 2H), 3.79 (s, 3H), 3.76 (t, 1H), 2.88 (dd, 1H), 2.75 (dd, 1H), 1.66 (m, 2H), 1.62 (s, 3H), 1.37 (m, 2H), 0.88 (t, 3H).

[0443]

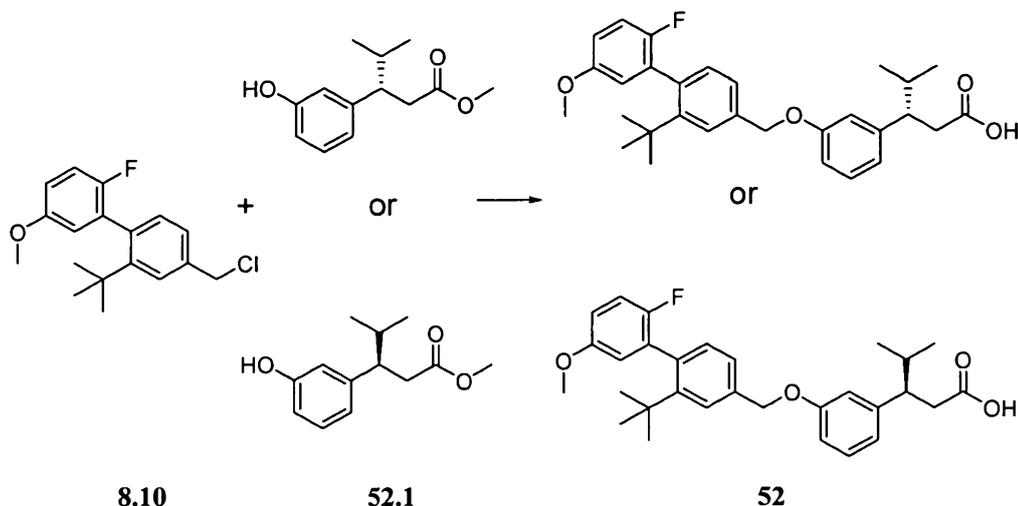
Example 51

[0444] **(3R)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-5-hexenoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-5-hexenoic acid (51).** Compound 43.4 (0.015 g, 0.068 mmol) was coupled with 8.10 (0.023 g, 0.075 mmol) according to the method described for preparation of 42 to afford 51 (0.029 g, 89%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.60 (d, 1H), 7.29 (dd, 1H), 7.24 (t, 1H), 7.05 (d, 1H), 7.00 (t, 1H), 6.84 (m, 4H), 6.77 (dd, 1H), 5.65 (m, 1H), 5.07 (s, 2H), 5.00 (m, 2H), 3.78 (s, 3H), 3.19 (m, 1H), 2.72 (dd, 1H), 2.61 (dd, 1H), 2.39 (t, 2H), 1.23 (s, 9H).

[0445]

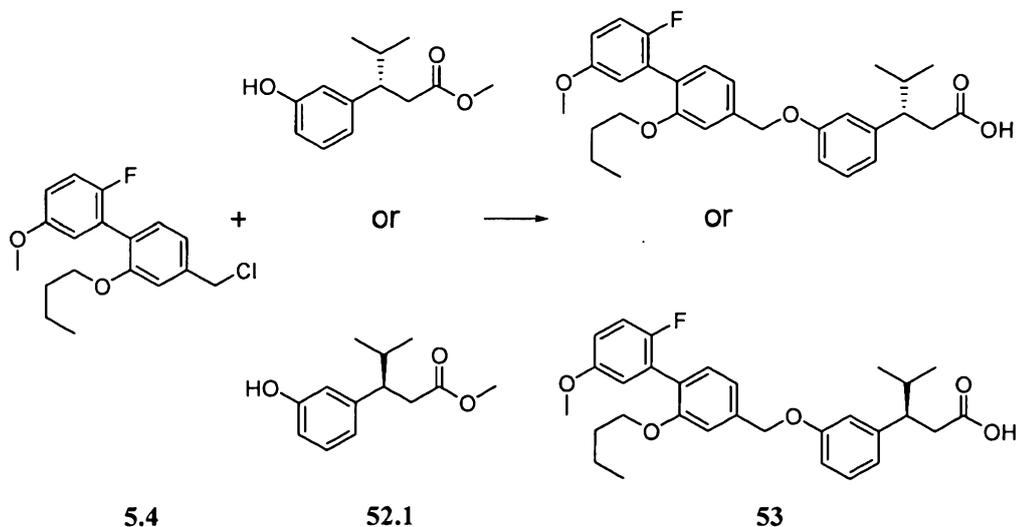
Example 52

[0446] **Methyl (3S)-3-(3-hydroxyphenyl)-4-methylpentanoate or methyl (3R)-3-(3-hydroxyphenyl)-4-methylpentanoate (52.1).** Compound 48.4 (0.10 g, 0.45 mmol) was hydrogenated according to the method described for preparation of 43.6 to afford 52.1 (0.10 g, 99%) as a colorless oil.



[0447] Compound (52). Compound **52.1** (0.015 g, 0.067 mmol) was coupled with **8.10** (0.023 g, 0.074 mmol) according to the method described for preparation of **42** to afford **52** (0.028 g, 87%) as a colorless oil. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 7.60 (d, 1H), 7.29 (dd, 1H), 7.21 (t, 1H), 7.04 (d, 1H), 6.99 (t, 1H), 6.85 (m, 2H), 6.78 (m, 3H), 5.07 (s, 2H), 3.78 (s, 3H), 2.86 (m, 1H), 2.79 (dd, 1H), 2.62 (dd, 1H), 1.84 (m, 1H), 1.23 (s, 9H), 0.93 (d, 3H), 0.76 (d, 3H).

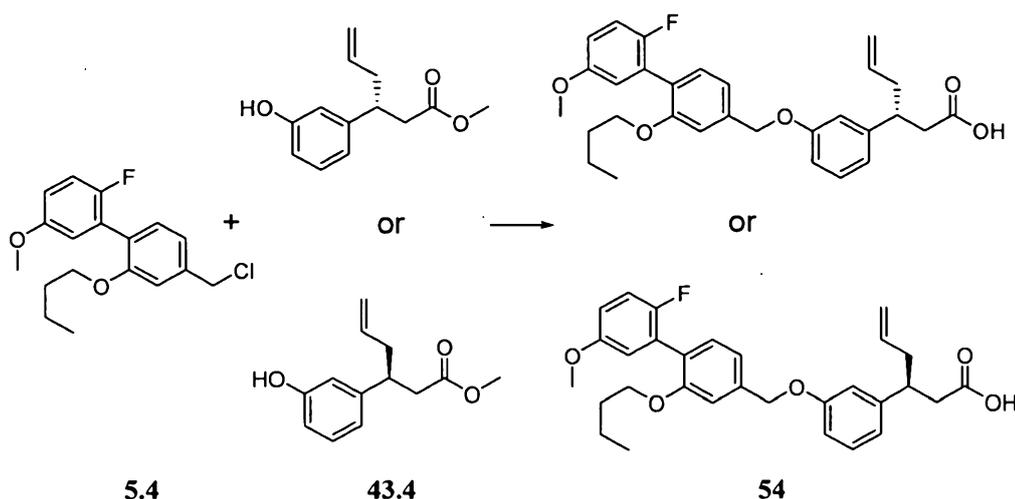
[0448] Example 53



[0449] (3S)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-methylpentanoic acid or (3R)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-

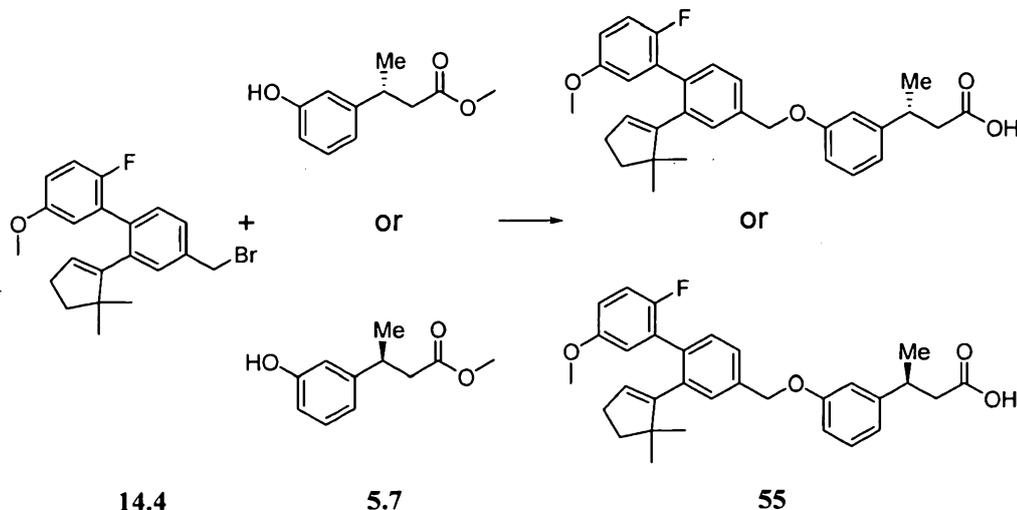
methylpentanoic acid (53). Compound **52.1** (0.015 g, 0.067 mmol) was coupled with **5.4** (0.024 g, 0.074 mmol) according to the method described for preparation of **42** to afford **53** (0.028 g, 83%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ ppm 7.28 (d, 1H), 7.21 (t, 1H), 7.06 (m, 2H), 7.02 (t, 1H), 6.82 (m, 5H), 5.06 (s, 2H), 3.98 (t, 2H), 3.79 (s, 3H), 2.86 (m, 1H), 2.79 (dd, 1H), 2.61 (dd, 1H), 1.85 (m, 1H), 1.66 (m, 2H), 1.37 (m, 2H), 0.93 (d, 3H), 0.88 (t, 3H), 0.76 (d, 3H).

[0450] **Example 54**



[0451] **(3R)-3-(3-(((2-(Butyloxy)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-5-hexenoic acid or (3S)-3-(3-(((2-(butyloxy)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-5-hexenoic acid (54).** Compound **43.4** (0.015 g, 0.068 mmol) was coupled with **5.4** (0.024 g, 0.075 mmol) according to the method described for preparation of **42** to afford **54** (0.026 g, 79%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ ppm 7.29 (d, 1H), 7.23 (t, 1H), 7.06 (m, 2H), 7.02 (t, 1H), 6.85 (m, 5H), 5.65 (m, 1H), 5.06 (s, 2H), 5.00 (m, 2H), 3.99 (t, 2H), 3.79 (s, 3H), 3.18 (m, 1H), 2.72 (dd, 1H), 2.60 (dd, 1H), 2.39 (t, 2H), 1.66 (m, 2H), 1.37 (m, 2H), 0.88 (t, 3H).

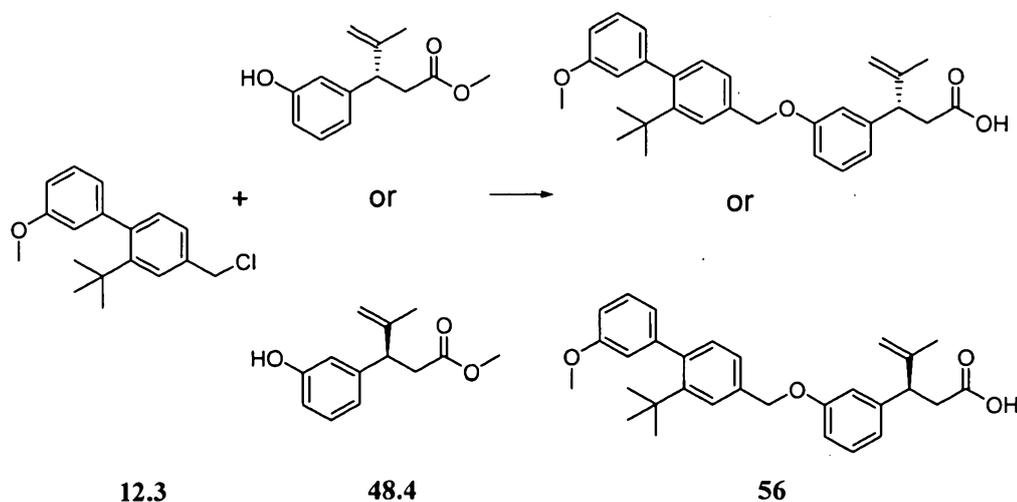
[0452]

Example 55

[0453]

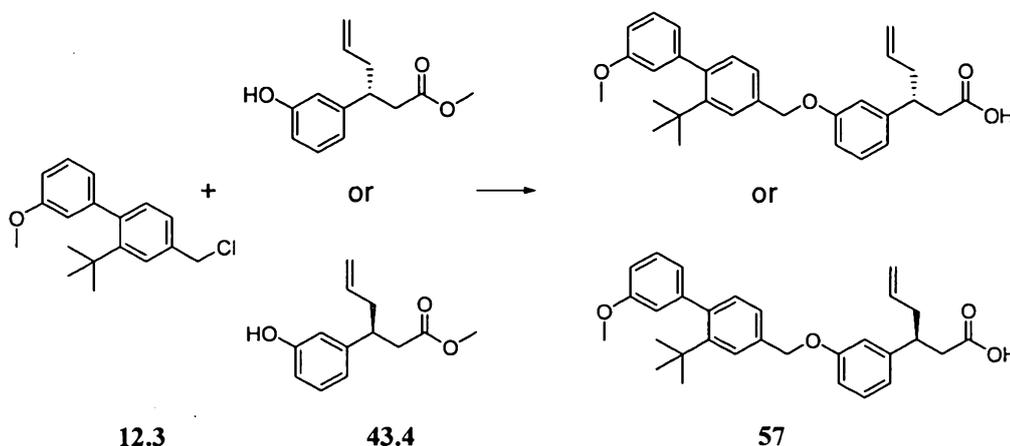
(3R)-3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (55). Compound 5.7 (0.012 g, 0.062 mmol) was coupled with 14.4 (0.026 g, 0.068 mmol) according to the method described for preparation of 42 to afford 55 (0.021 g, 71%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.39 (dd, 1H), 7.33 (d, 1H), 7.29 (bd, 1H), 7.24 (t, 1H), 6.96 (t, 1H), 6.86 (m, 3H), 6.79 (m, 2H), 5.52 (bt, 1H), 5.08 (s, 2H), 3.75 (s, 3H), 3.26 (m, 1H), 2.68 (dd, 1H), 2.57 (dd, 1H), 2.24 (dt, 2H), 1.65 (t, 2H), 1.32 (d, 3H), 0.85 (s, 6H).

[0454]

Example 56

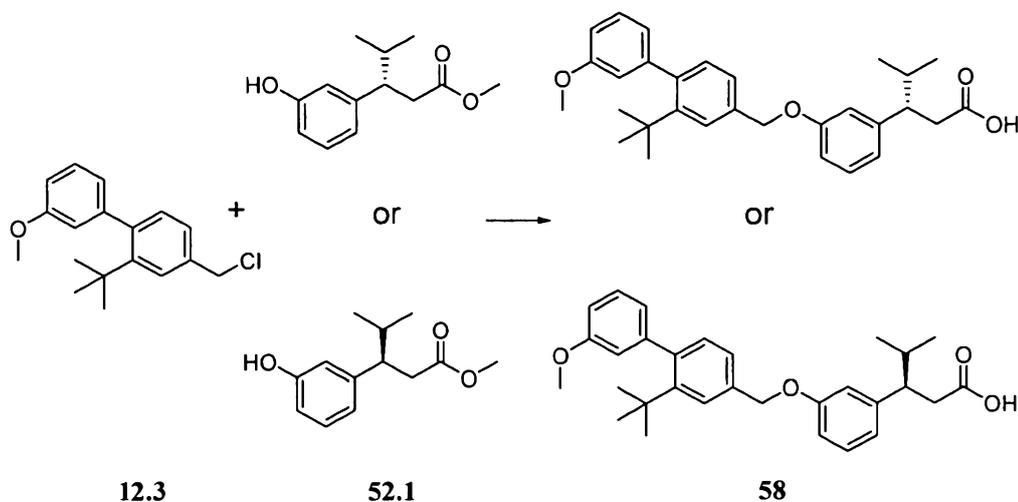
[0455] (3S)-3-(3-(((2-(1,1-Dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-methyl-4-pentenoic acid or (3R)-3-(3-(((2-(1,1-dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-methyl-4-pentenoic acid (**56**). Compound **48.4** (0.015 g, 0.068 mmol) was coupled with **12.3** (0.022 g, 0.075 mmol) according to the method described for preparation of **42** to afford **56** (0.028 g, 89%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.56 (d, 1H), 7.24 (m, 3H), 7.05 (d, 1H), 6.86 (m, 6H), 5.06 (s, 2H), 4.93 (s, 1H), 4.90 (bt, 1H), 3.81 (s, 3H), 3.76 (t, 1H), 2.89 (dd, 1H), 2.75 (dd, 1H), 1.62 (s, 3H), 1.22 (s, 9H).

[0456] **Example 57**



[0457] (3R)-3-(3-(((2-(1,1-dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-5-hexenoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-5-hexenoic acid (**57**). Compound **43.4** (0.015 g, 0.068 mmol) was coupled with **12.3** (0.022 g, 0.075 mmol) according to the method described for preparation of **42** to afford **57** (0.027 g, 88%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.57 (d, 1H), 7.24 (m, 3H), 7.05 (d, 1H), 6.87 (m, 4H), 6.82 (m, 2H), 5.65 (m, 1H), 5.06 (s, 2H), 5.00 (m, 2H), 3.81 (s, 3H), 3.19 (m, 1H), 2.72 (dd, 1H), 2.61 (dd, 1H), 2.39 (t, 2H), 1.22 (s, 9H).

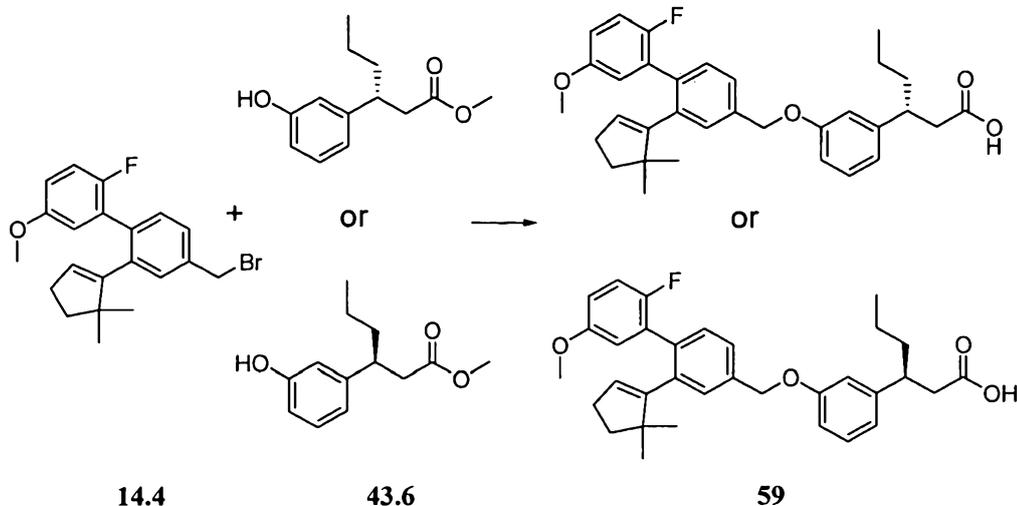
[0458]

Example 58

[0459] **(3S)-3-(3-(((2-(1,1-Dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-methylpentanoic acid or (3R)-3-(3-(((2-(1,1-dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-methylpentanoic acid (58).**

Compound **52.1** (0.015 g, 0.067 mmol) was coupled with **12.3** (0.021 g, 0.074 mmol) according to the method described for preparation of **42** to afford **58** (0.028 g, 91%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.57 (d, 1H), 7.25 (m, 2H), 7.21 (t, 1H), 7.04 (d, 1H), 6.87 (m, 3H), 6.81 (m, 2H), 6.77 (d, 1H), 5.06 (s, 2H), 3.81 (s, 3H), 2.87 (m, 1H), 2.79 (dd, 1H), 2.62 (dd, 1H), 1.85 (m, 1H), 1.21 (s, 9H), 0.93 (d, 3H), 0.76 (d, 3H).

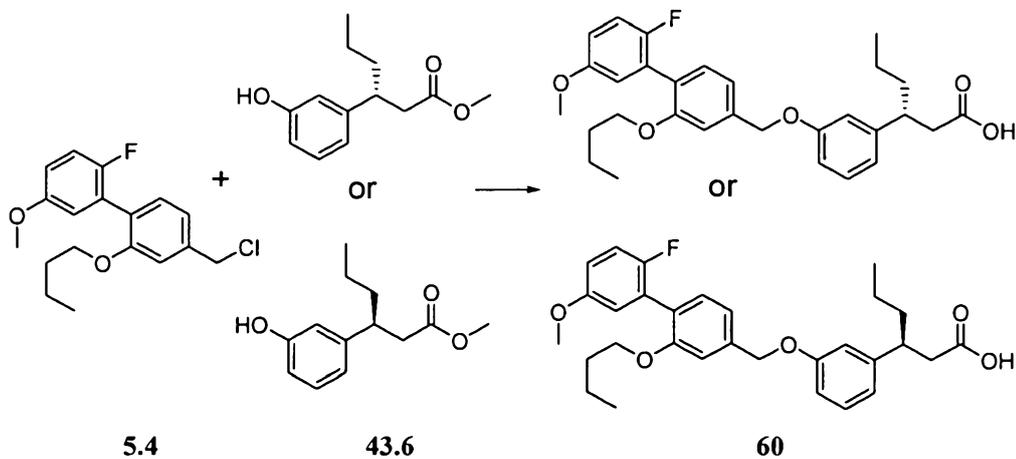
[0460]

Example 59

[0461]

(3R)-3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (59). Compound 43.6 (0.015 g, 0.067 mmol) was coupled with 14.4 (0.029 g, 0.074 mmol) according to the method described for preparation of 42 to afford 59 (0.020 g, 58%) as a colorless oil. ^1H NMR (400 MHz, CDCl_3) δ ppm 7.39 (dd, 1H), 7.33 (d, 1H), 7.29 (d, 1H), 7.22 (t, 1H), 6.96 (t, 1H), 6.82 (m, 5H), 5.52 (bt, 1H), 5.08 (s, 2H), 3.75 (s, 3H), 3.07 (m, 1H), 2.62 (m, 2H), 2.24 (dt, 2H), 1.65 (t, 2H), 1.60 (m, 2H), 1.18 (m, 2H), 0.85 (m, 9H).

[0462]

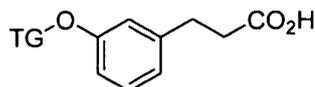
Example 60

[0463] (3R)-3-(3-(((2-(Butyloxy)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-(butyloxy)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (60). Compound 43.6 (0.015 g, 0.067 mmol) was coupled with 5.4 (0.024 g, 0.074 mmol) according to the method described for preparation of 42 to afford 60 (0.027 g, 83%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.29 (d, 1H), 7.23 (t, 1H), 7.06 (m, 2H), 7.02 (t, 1H), 6.84 (m, 5H), 5.07 (s, 2H), 3.99 (t, 2H), 3.79 (s, 3H), 3.08 (m, 1H), 2.63 (m, 2H), 1.65 (m, 2H), 1.61 (m, 2H), 1.37 (m, 2H), 1.18 (m, 2H), 0.88 (t, 3H), 0.85 (t, 3H).

[0464] **Example 61**

[0465] The following compounds were prepared from commercially available methyl 3-(3-hydroxyphenyl)propanoate (available from Agile Labs Division of Tyger Scientific) and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein.

Table 1



Compound	TG	Compound	TG
61.1		61.2	
61.3		61.4	

[0466] 3-(3-(((2-(2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (61.1). MS ESI (neg.) m/e: 475.1 (M-H).

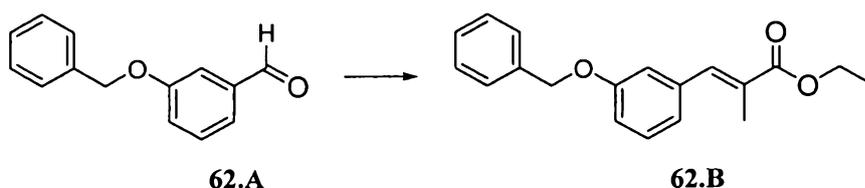
[0467] 3-(3-(((2-(2,2-Dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (61.2). MS ESI (neg.) m/e: 425.2 (M-H).

[0468] 3-(3-(((2-(2,2-Dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (61.3). MS ESI (neg.) m/e: 455.3 (M-H).

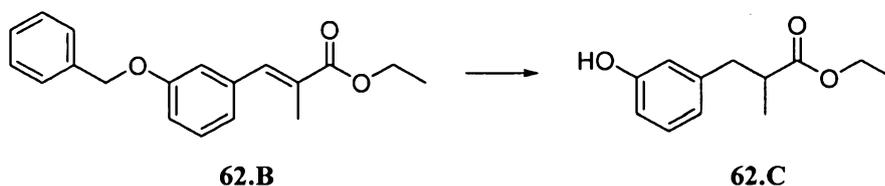
[0469] 3-(3-(((2-(1,1-Dimethylethyl)-3'-(methylsulfanyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (61.4). MS ESI (neg.) m/e: 433.1 (M-H).

[0470] **Example 62**

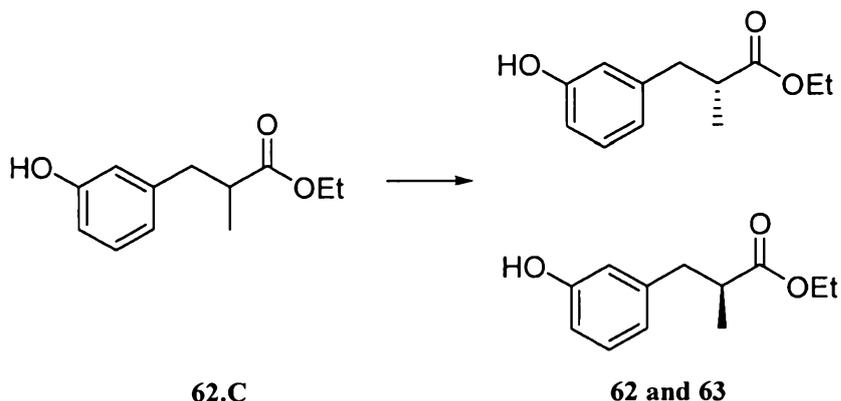
[0471] **Synthesis of methyl (2R)-3-(3-hydroxyphenyl)-2-methylpropanoate (62) and methyl (2S)-3-(3-hydroxyphenyl)-2-methylpropanoate (63).**



[0472] **(E)-Ethyl 3-(3-(benzyloxy)phenyl)-2-methylacrylate (62.B).** To a solution of (carboethoxyethylidene)triphenylphosphorane (available from Aldrich)(5.50 g, 15.2 mmol) in THF (25 mL) was added 3-(benzyloxy)benzaldehyde (available from Aldrich)(2.93 g, 13.8 mmol) in THF (10 mL) under nitrogen at -78°C . The reaction was allowed to slowly warm to room temperature and stirred for 2 hours. EtOAc (100 mL) was added, and the mixture was washed with brine (30 x 2 mL). The organic layer was dried over MgSO_4 . The solvent was removed by evaporation. The crude product was purified by passing through a short silica gel column, eluting with hexane/EtOAc (85/15) to give (E)-ethyl 3-(3-(benzyloxy)phenyl)-2-methylacrylate **62.B**.



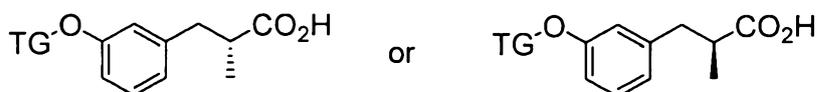
[0473] **Ethyl 3-(3-hydroxyphenyl)-2-methylpropanoate (62.C).** A mixture of (E)-ethyl 3-(3-(benzyloxy)phenyl)-2-methylacrylate **62.B** (0.93 g, 3.1 mmol) and palladium on charcoal (10%, 0.1 g) in EtOH (25.0 mL) was flushed with hydrogen three times. The reaction mixture was stirred at room temperature for 2-3 hours. The catalyst was filtered away, and the solvent was removed. The residue, ethyl 3-(3-hydroxyphenyl)-2-methylpropanoate **62.C** was used in the next step without further purification.



[0474] Methyl (2R)-3-(3-hydroxyphenyl)-2-methylpropanoate (**62**) and methyl (2S)-3-(3-hydroxyphenyl)-2-methylpropanoate (**63**). Racemic ethyl 3-(3-hydroxyphenyl)-2-methylpropanoate **62.C** (0.40 g) was separated by ChiralPak OJ-H column, eluted with 10% isopropanol in hexane to give the separated enantiomers; (R)-ethyl 3-(3-hydroxyphenyl)-2-methylpropanoate and (S)-ethyl 3-(3-hydroxyphenyl)-2-methylpropanoate **62** and **63**. MS ESI (pos.) m/e: 209.1 (M+H)⁺.

[0475] The following compounds were prepared from **62** and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Both of the compounds in the following table were prepared using the same enantiomer of the phenol.

Table 2



Compound	TG	Compound	TG
62.1		62.2	

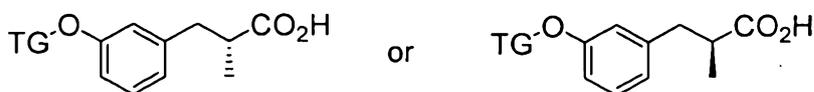
[0476] (2R)-3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-2-methylpropanoic acid or (2S)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-2-methylpropanoic acid (**62.1**). MS ESI (neg.) m/e: 487.1 (M-H).

[0477] (2R)-3-(3-(((2-(2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-2-methylpropanoic acid or (2S)-3-(3-(((2-(2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-2-methylpropanoic acid (62.2). MS ESI (neg.) m/e: 489.2 (M-H).

[0478] **Example 63**

The following compounds were prepared from 63 and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Both of the compounds in the following table were prepared using the same enantiomer of the phenol.

Table 3



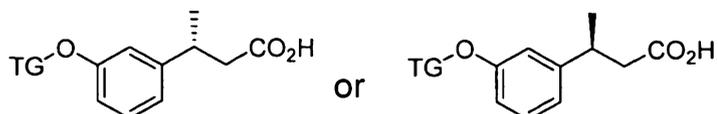
Compound	TG	Compound	TG
63.1		63.2	

[0479] (2S)-3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-2-methylpropanoic acid or (2R)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-2-methylpropanoic acid (63.1). MS ESI (neg.) m/e: 487.1 (M-H).

[0480] (2S)-3-(3-(((2-(2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-2-methylpropanoic acid or (2R)-3-(3-(((2-(2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-2-methylpropanoic acid (63.2). MS ESI (neg.) m/e: 489.2 (M-H).

[0481] **Example 64**

[0482] The following compounds were prepared from 5.7 and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Each of the compounds in the following table were prepared using the same enantiomer of the phenol.

Table 4

Compound	TG	Compound	TG
64.1		64.2	
64.3		64.4	
64.5		64.6	
64.7		64.8	

Compound	TG	Compound	TG
64.9		64.10	
64.11		64.12	
64.13		64.14	
64.15		64.16	
64.17		64.18	
64.19		64.20	

Compound	TG	Compound	TG
64.21		64.22	
64.23		64.24	
64.25		64.26	

[0483] (3R)-3-(3-(((2-((2,2-Dimethylpropyl)oxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-((2,2-dimethylpropyl)oxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.1). Example 64.1 was synthesized from 27.1 by a method analogous to that used to prepare compound 27 using 1-bromo-2,2-dimethylpropane (commercially available from Aldrich). MS ESI (neg.) m/e: 479.2 (M-H).

[0484] (3R)-3-(3-(((2-(Butyloxy)-3'-(methylsulfanyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(butyloxy)-3'-(methylsulfanyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.2). Example 64.2 was synthesized from 20.4 by a method analogous to that used to prepare compound 21 using 3-(methylthio)phenylboronic acid (commercially available from Aldrich). MS ESI (neg.) m/e: 463.1 (M-H).

- [0485] (3R)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5-methyl-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5-methyl-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.3). MS ESI (neg.) m/e: 463.1 (M-H).
- [0486] (3R)-3-(3-(((2-((1E)-3,3-Dimethyl-1-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-((1E)-3,3-dimethyl-1-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.4). MS ESI (neg.) m/e: 951.4 (2M-H)⁺, 475.1 (M-H)⁺.
- [0487] (3R)-3-(3-(((2-(4,4-Dimethyl-1-cyclohexen-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(4,4-dimethyl-1-cyclohexen-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.5). MS ESI (neg.) m/e: 501.2 (M-H)⁺.
- [0488] (3R)-3-(3-(((2-(3,3-Dimethylbutyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(3,3-dimethylbutyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.6). MS ESI (neg.) m/e: 955.5 (2M-H)⁺, 477.2 (M-H)⁺.
- [0489] (3R)-3-(3-(((2-(4,4-Dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(4,4-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.7). MS ESI (neg.) m/e: 503.2 (M-H)⁺.
- [0490] (3R)-3-(3-(((2'-(Fluoro-5'-(methoxy)-2-((1E)-1-pentenyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2'-(fluoro-5'-(methoxy)-2-((1E)-1-pentenyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.8). MS ESI (neg.) m/e: 923.3 (2M-H)⁺, 461.2 (M-H)⁺..
- [0491] (3R)-3-(3-(((2-((E)-2-Cyclohexylethenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-((E)-2-cyclohexylethenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.9). MS ESI (neg.) m/e: 501.1 (M-H)⁺.
- [0492] (3R)-3-(3-(((2-(1,1-Dimethylethyl)-2',3-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-2',3-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.10). MS ESI (neg.) m/e: 935.3 (2M-H)⁺, 467.2 (M-H)⁺.

- [0493] (3R)-3-(3-(((2-(1,1-Dimethylbutyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(1,1-dimethylbutyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.11). MS ESI (neg.) m/e: 955.5 (2M-H)⁺, 477.2 (M-H)⁺.
- [0494] (3R)-3-(3-(((2-(1-Cyclohepten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(1-cyclohepten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.12). MS ESI (neg.) m/e: 975.4 (2M-H)⁺, 487.2 (M-H)⁺.
- [0495] (3R)-3-(3-(((2-(4-(1,1-Dimethylethyl)-1-cyclohexen-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(4-(1,1-dimethylethyl)-1-cyclohexen-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.13). MS ESI (neg.) m/e: 529.3 (M-H)⁺.
- [0496] (3R)-3-(3-(((2'-Fluoro-5'-(methoxy)-2-pentyl-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2'-fluoro-5'-(methoxy)-2-pentyl-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.14). MS ESI (neg.) m/e: 927.4 (2M-H)⁺, 463.1 (M-H)⁺.
- [0497] (3R)-3-(3-(((2-(2-Cyclohexylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(2-cyclohexylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.15). MS ESI (neg.) m/e: 503.2 (M-H)⁺.
- [0498] (3R)-3-(3-(((2'-Fluoro-5'-(methoxy)-2-tricyclo[3.3.1.1~3,7~]dec-1-yl-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2'-fluoro-5'-(methoxy)-2-tricyclo[3.3.1.1~3,7~]dec-1-yl-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.16). MS ESI (neg.) m/e: 527.2 (M-H)⁺.
- [0499] (3R)-3-(3-(((2-Cycloheptyl-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-cycloheptyl-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.17). MS ESI (neg.) m/e: 979.5 (2M-H)⁺, 489.2 (M-H)⁺.
- [0500] (3R)-3-(3-(((2'-Fluoro-2-(1-methylcyclopropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2'-fluoro-2-(1-methylcyclopropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.18). MS ESI (neg.) m/e: 895.5 (2M-H)⁺, 447.3 (M-H)⁺.

[0501] (3R)-3-(3-(((2-(1-Cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.19). MS ESI (neg.) m/e: 459.1 (M-H).

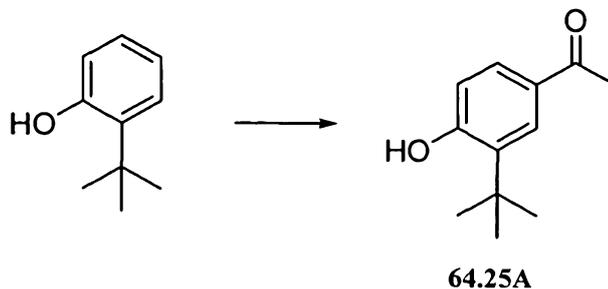
[0502] (3R)-3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.20). MS ESI (neg.) m/e: 469.3 (M-H).

[0503] (3R)-3-(3-(((2-(1-Cyclohexen-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(1-cyclohexen-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.21). MS ESI (neg.) m/e: 473.2 (M-H).

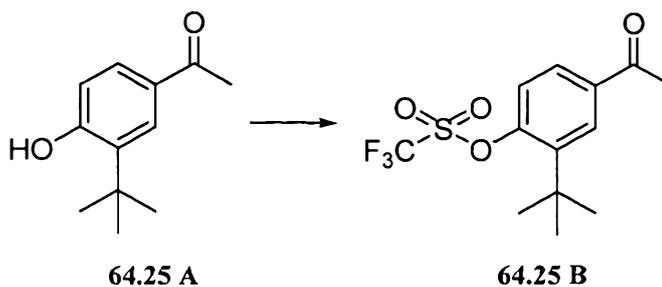
[0504] (3R)-3-(3-(((2-(2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.22). MS ESI (neg.) m/e: 489.2 (M-H).

[0505] (3R)-3-(3-(((2-(1,1-Dimethylethyl)-3'-(methylsulfanyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-3'-(methylsulfanyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.23). MS ESI (neg.) m/e: 447.1 (M-H). ¹H NMR (500 MHz) (CDCl₃) δ ppm 7.62 (1 H, d, J=1.2 Hz), 7.32 (4 H, m), 7.20 (1 H, s), 7.10 (2 H, m), 6.95 (2 H, m), 6.89 (1 H, d, J=7.6 Hz), 5.11 (2 H, s), 3.35 (1 H, m), 2.76 (1 H, m), 2.65 (1 H, m), 2.51 (3 H, s), 1.36 (3 H, d, J=7.1 Hz), 1.25 (9 H, s).

[0506] (3R)-3-(3-(((2-(1,1-Dimethylethyl)-3'-(ethoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-3'-(ethoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.24). MS ESI (neg.) m/e: 445.1 (M-H). ¹H NMR (500 MHz) (CDCl₃) δ ppm 7.60 (1 H, d, J=1.2 Hz), 7.29 (3 H, m), 7.07 (1 H, d, J=7.8 Hz), 6.93 (5 H, m), 6.84 (1 H, d, J=1.7 Hz), 5.09 (2 H, s), 4.06 (2 H, ddd, J=13.4, 6.6, 6.4 Hz), 3.33 (1 H, m), 2.74 (1 H, m), 2.63 (1 H, m), 1.44 (3 H, t, J=7.0 Hz), 1.35 (3 H, d, J=7.1 Hz), 1.25 (9 H, s).

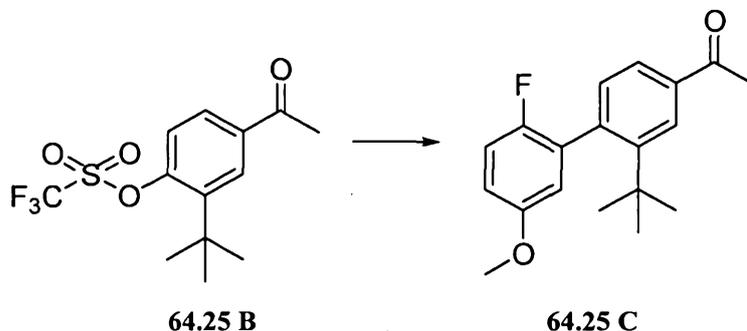
[0507] Example 64.25

[0508] 1-(3-(1,1-Dimethylethyl)-4-hydroxyphenyl)ethanone (64.25 A). To a dry, round bottom flask was added aluminum chloride (4.402g, 33.0 mmol). The flask was then cooled to -45°C . After 10 minutes, dry toluene (80 mL) was added followed by dropwise addition of 2-tert-butylphenol (5.00 mL, 32.7 mmol)(commercially available from Aldrich). The mixture was stirred and maintained at -4°C . After 1.5 hours, acetyl chloride (2.40 mL, 33.8 mmol) was carefully added dropwise. The mixture was allowed to warm to room temperature and monitored with TLC and LC-MS. After 18 hours, the mixture was slowly poured onto crushed ice. This mixture was stirred at room temperature and the crystals were collected by filtration. The light yellow solid was identified as **64.25 A** (4.2589 g, 68%). MS ESI (pos.) m/e: 193.1 (M+H)⁺.

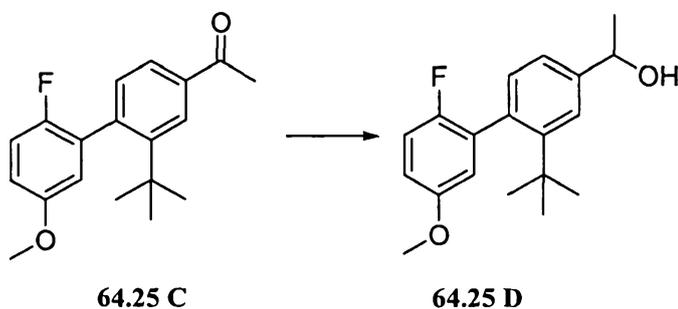


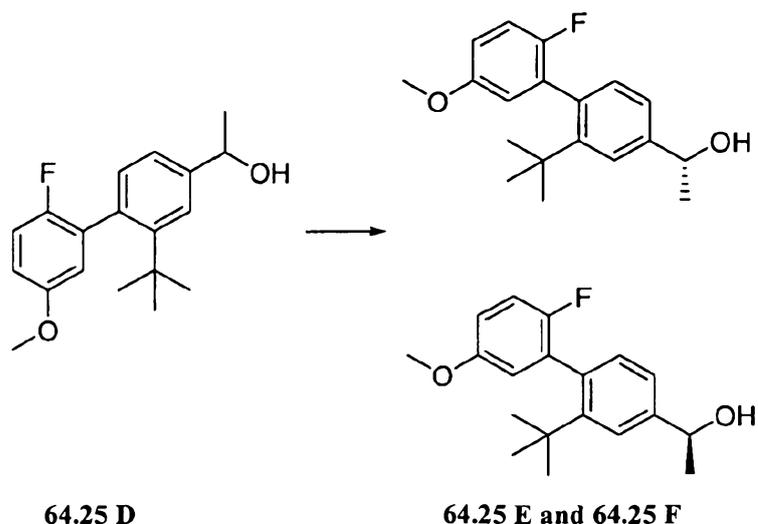
[0509] 4-Acetyl-2-(1,1-dimethylethyl)phenyl trifluoromethanesulfonate (64.25 B). To a stirred solution of **64.25 A** (2.0006 g, 10.41 mmol) in dry DCM (37 mL) was added TEA (3.0 mL, 21.57 mmol) and DMAP (0.1309 g, 1.071 mmol). After 20 minutes, N-phenyltrifluoromethanesulfonimide (5.5846 g, 15.63 mmol) was added in portions. Upon complete addition, the solution was stirred at room temperature and monitored with TLC and LC-MS. After 4.5 hours, the reaction was diluted with brine and extracted three times with DCM. After drying over anhydrous magnesium sulfate and filtration, the solvent was removed under reduced pressure. The residue was purified

by silica gel flash chromatography (0-20% EtOAc/hexane) to yield **64.25 B** (3.0227 g, 90 % yield). MS ESI (pos.) m/e: 325.1 (M+H)⁺.

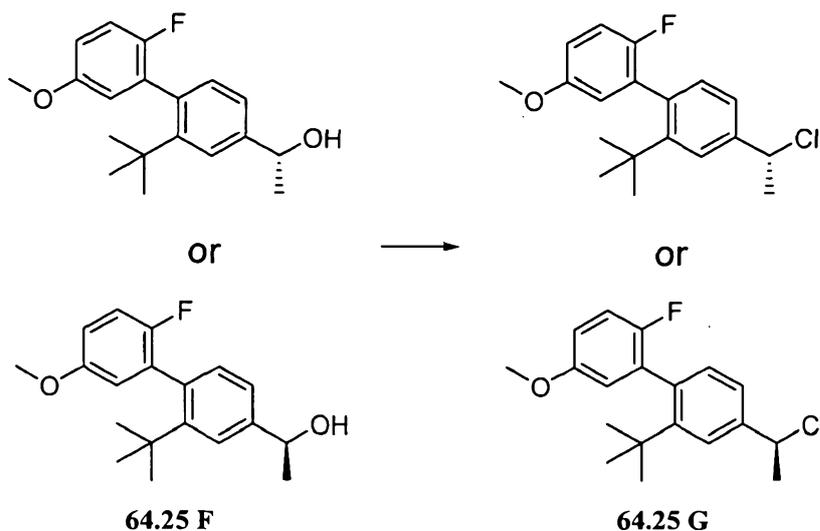


[0510] **1-(2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)ethanone (64.25 C)**. A dry round bottom containing **64.25 B** (3.0227 g, 9.3202 mmol), 2-fluoro-5-methoxyphenylboronic acid (2.4005 g, 14.125 mmol)(commercially available from Aldrich), tetrakis(triphenylphosphine)palladium (1.0853 g, 0.93920 mmol), and potassium carbonate (3.9996 g, 28.940 mmol) was evacuated and backfilled three times with argon. Dry DMF (25 mL) was added via syringe under argon, then the mixture was heated to 100 °C and monitored with TLC. After 3 hours, the reaction was cooled to room temperature, then diluted with water. The mixture was extracted three times with EtOAc then concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (0-15% EtOAc/hexane) to yield **64.25 C** (2.6053 g, 93 % yield). MS ESI (pos.) m/e: 301.1 (M+H)⁺.

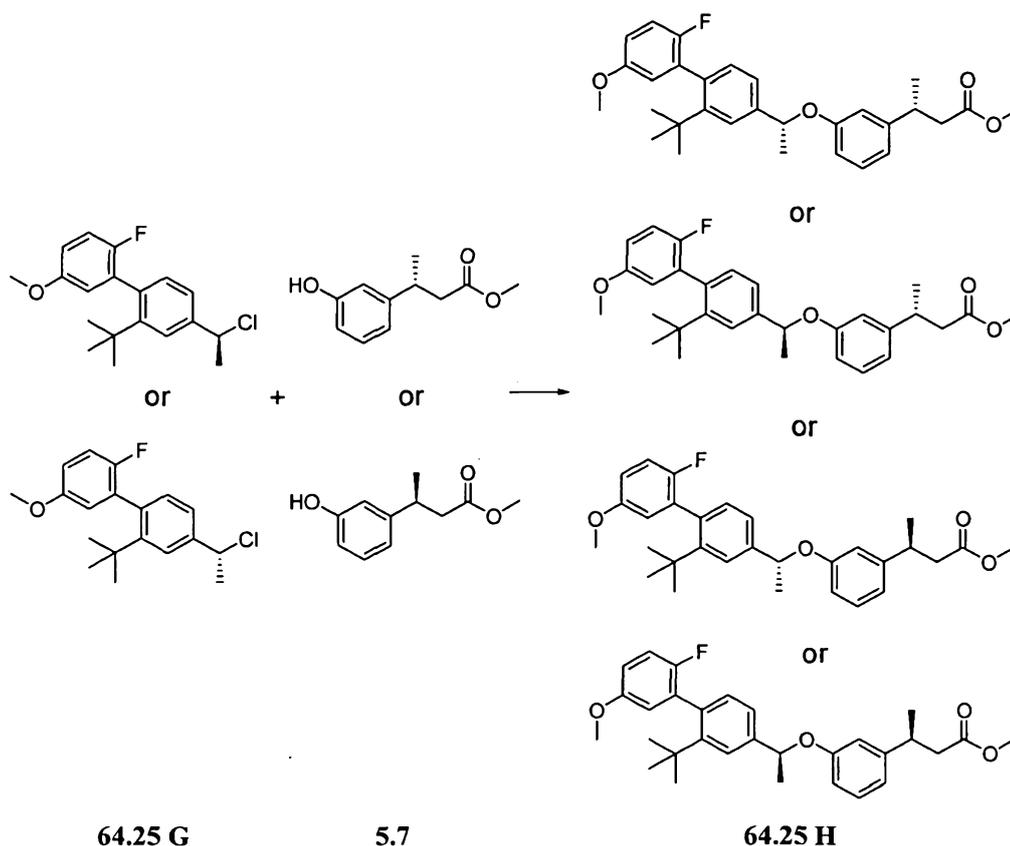




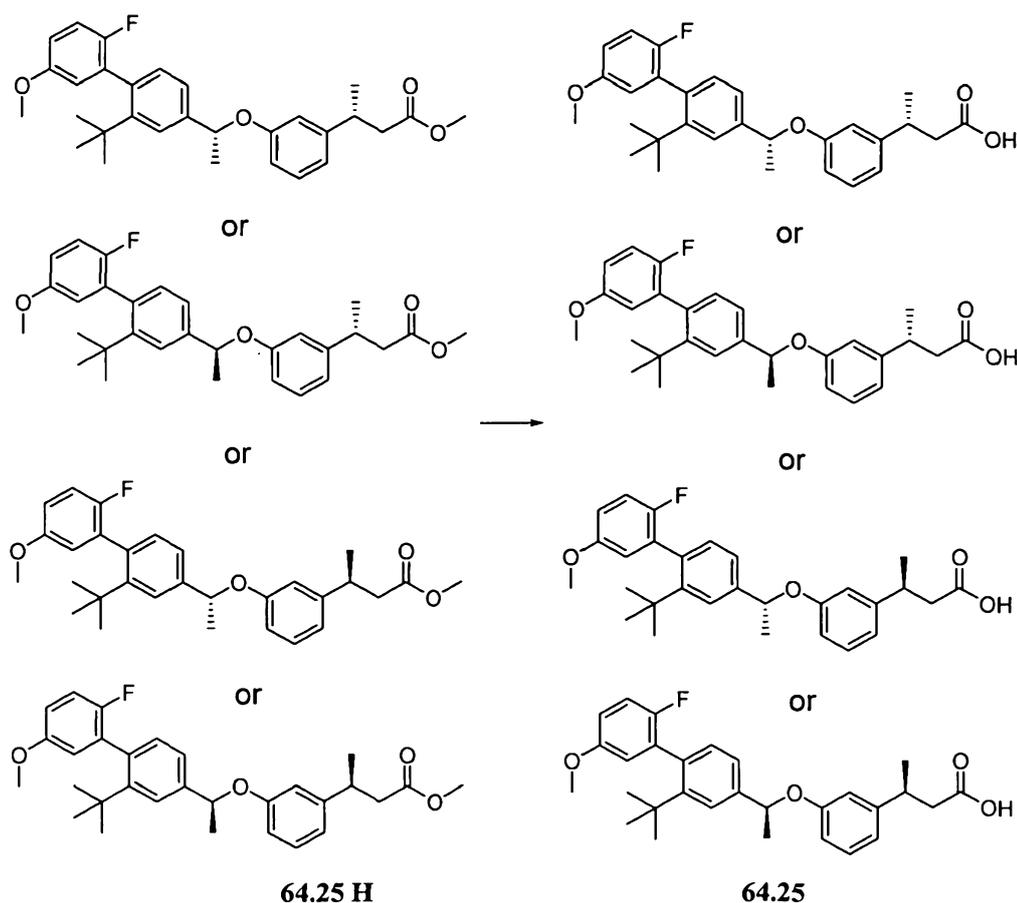
[0511] **1-(2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)ethanol (64.25 D)**. To a dry round bottom flask containing **64.25 C** (2.5921 g, 8.630 mmol) was added a premixed solution of dry MeOH (10 mL) and dry DCM (10 mL). After stirring at 0 °C for ~15 minutes, sodium borohydride (0.6632 g, 17.53 mmol) was carefully added at 0 °C. Upon complete addition, the reaction was allowed to warm to room temperature. After 2 hours, the reaction was cooled in an ice bath, then carefully quenched with water and extracted three times with DCM. After drying over anhydrous magnesium sulfate and filtration, the organic solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (0-15% EtOAc/hexane) to yield **64.25 D** (2.5329 g, 97 % yield). MS ESI (pos.) m/e: 285.1 (M-H₂O)⁺. Chiral separation of **64.25 D** was accomplished using SFC with 9 g/min MeOH(0.6% DEA) + 81 g/min CO₂ on a 250 x 30 mm OD-H column. The outlet pressure of the system was set to 140 bar, temperature at 25 °C and detector wavelength was 220 nm. Sample was dissolved to 54 mg/mL in MeOH and separations on 13.5 mg injections were performed at a rate of one injection per 1.65 minutes to provide **64.25 E** (peak 1) and **64.25 F** (peak 2). Both enantiomers were used to synthesize example compounds, and both enantiomers gave active compounds.



[0512] **4-((1S)-1-Chloroethyl)-2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl or 4-((1R)-1-chloroethyl)-2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (64.25 G).** A dry, round bottom flask containing **64.25 F** (1.0221 g, 3.380 mmol) was evacuated and backfilled with argon. Dry DCM (14 mL) was added under argon, and the homogeneous solution was cooled to 0 °C. After 15 minutes, thionyl chloride (1.0 mL, 13.71 mmol) was carefully added dropwise at 0 °C. Upon complete addition of thionyl chloride, the mixture was allowed to warm to room temperature and stirred overnight. After 2.5 hours, the reaction was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (0-15% EtOAc/hexane) to yield **64.25 G** (744.7 mg, 69 % yield). MS ESI (pos.) m/e: 338.2 (M+H₂O)⁺.



[0513] **Methyl (3R)-3-(3-(((1R)-1-(2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)ethyl)oxy)phenyl)butanoate or methyl (3R)-3-(3-(((1S)-1-(2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)ethyl)oxy)phenyl)butanoate or methyl (3S)-3-(3-(((1R)-1-(2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)ethyl)oxy)phenyl)butanoate or methyl (3S)-3-(3-(((1S)-1-(2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)ethyl)oxy)phenyl)butanoate (64.25 H).** To a round bottom flask containing 5.7 (0.0276 g, 0.142 mmol) in 2.0 mL dry DMF was added cesium carbonate (0.0510 g, 0.157 mmol). The mixture was stirred at room temperature for 15 minutes, then 64.25 G (0.0508 g, 0.158 mmol) was added. After 18 hours, the reaction was diluted with water then extracted five times with EtOAc. The organic extraction was then washed one time with brine and dried over anhydrous magnesium sulfate. The solid was filtered off, and the solvent was concentrated. The residue was purified by silica gel flash chromatography (0-40 % EtOAc/hexane) to yield 64.25 H (41.5 mg, 61 % yield). MS ESI (pos.) m/e: 501.2 (M+Na)⁺.



[0514] (3R)-3-(3-(((1R)-1-(2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)ethyl)oxy)phenyl)butanoic acid, (3R)-3-(3-(((1S)-1-(2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)ethyl)oxy)phenyl)butanoic acid, (3S)-3-(3-(((1R)-1-(2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)ethyl)oxy)phenyl)butanoic acid, or (3S)-3-(3-(((1S)-1-(2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)ethyl)oxy)phenyl)butanoic acid (64.25). A pre-mixed solution of 2M sodium hydroxide (1 mL, 2.0 mmol), MeOH (1 mL), and THF (1 mL, 0.087 mmol) was added to a round bottom flask containing 64.25 H (0.0415 g, 0.087 mmol). The resulting solution was stirred at room temperature and monitored with TLC and LC-MS. After 24 hours, the mixture was diluted with water and acidified with 2M HCl to a pH 6. The mixture was then extracted five times with EtOAc. The organic phase was dried over anhydrous magnesium sulfate then filtered and concentrated in vacuo. The residue was purified by silica gel flash chromatography (0-100 % EtOAc/hexane) to yield 64.25 (31.1 mg, 77 %

yield). (MS ESI (neg.) m/e: 445.1 (M-H). ¹H NMR (500 MHz) (CDCl₃) δ ppm 7.60 (1 H, d, *J*=1.2 Hz), 7.29 (3 H, m), 7.07 (1 H, d, *J*=7.8 Hz), 6.93 (5 H, m), 6.84 (1 H, d, *J*=1.7 Hz), 5.09 (2 H, s), 4.06 (2 H, ddd, *J*=13.4, 6.6, 6.4 Hz), 3.33 (1 H, m), 2.74 (1 H, m), 2.63 (1 H, m), 1.44 (3 H, t, *J*=7.0 Hz), 1.35 (3 H, d, *J*=7.1 Hz), 1.25 (9 H, s).

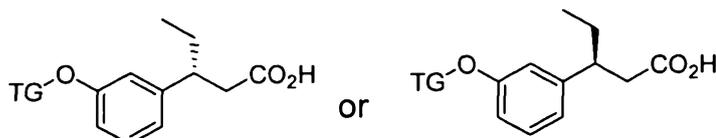
[0515] **(3R)-3-(3-(((2-(butyloxy)-3'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-3-(3-(((2-(butyloxy)-3'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (64.26).** Example 64.26 was synthesized from 20.4 by a method analogous to that used to prepare compound 21 using 3-fluorophenylboronic acid (commercially available from Aldrich). MS ESI (neg.) m/e: 435.2 (M-H).

[0516] **Example 65**

[0517] The following compounds were prepared from 17.1 and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein.

Both of the compounds in the following table were prepared using the same enantiomer of the phenol.

Table 5



Compound	TG	Compound	TG
65.1		65.2	

[0518] **(3R)-3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid (65.1).** MS ESI (neg.) m/e: 501.2 (M-H).

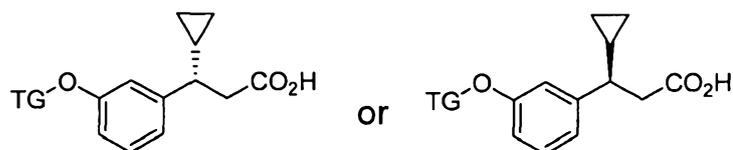
[0519] **(3R)-3-(3-(((2-(Butyloxy)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-(butyloxy)-3'-(methoxy)-1,1'-**

biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid (65.2). MS ESI (neg.) m/e: 461.2 (M-H).

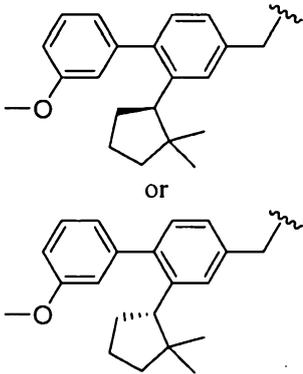
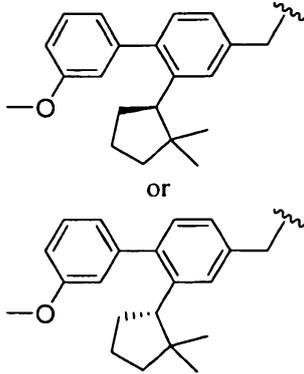
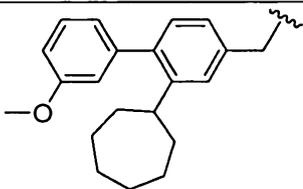
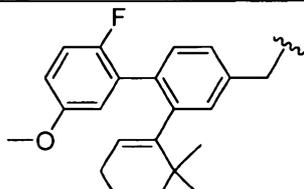
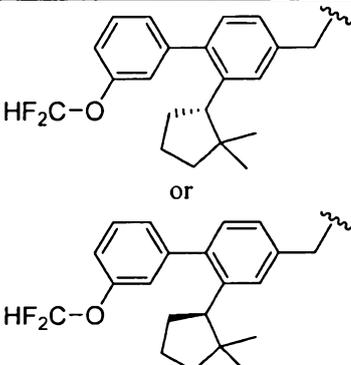
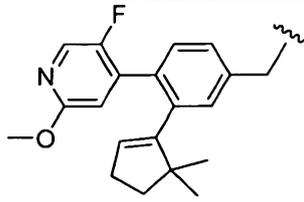
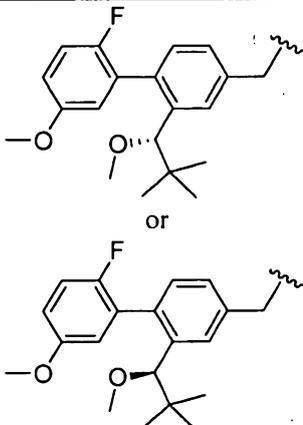
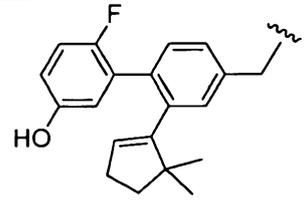
[0520] Example 66

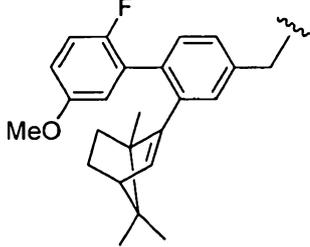
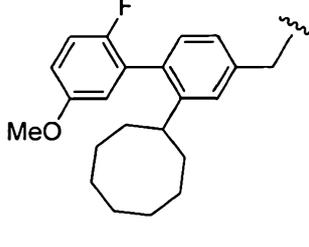
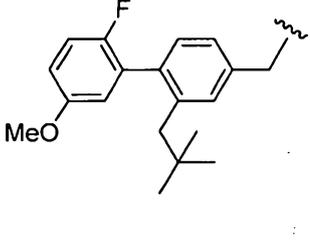
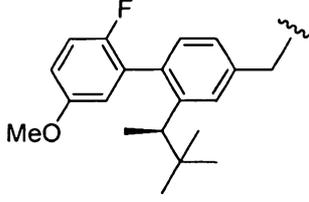
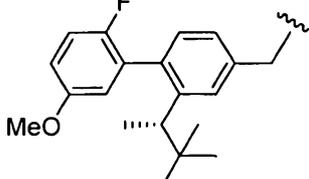
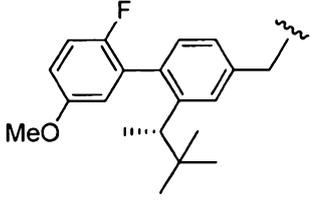
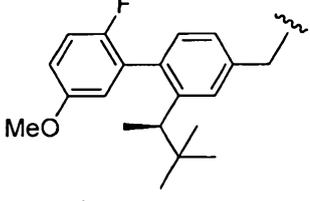
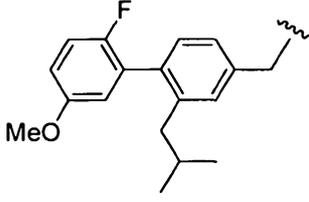
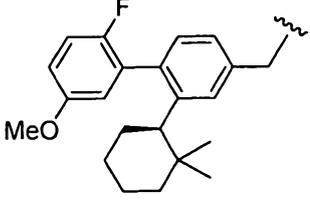
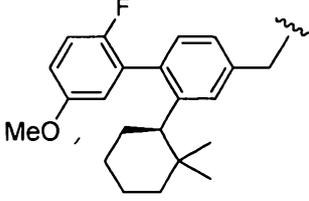
[0521] The following compounds were prepared from 8.4 or 66.6X and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Each of the compounds in the following table were prepared using the same enantiomer of the phenol.

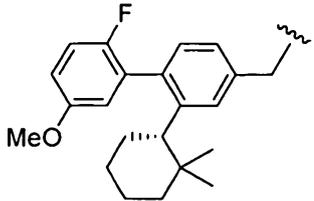
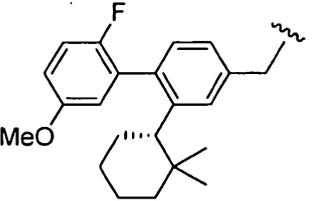
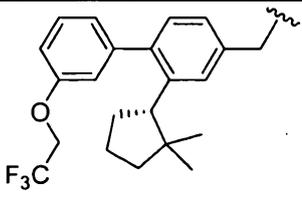
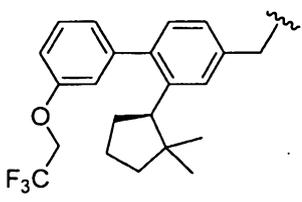
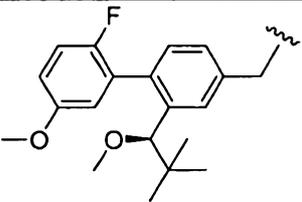
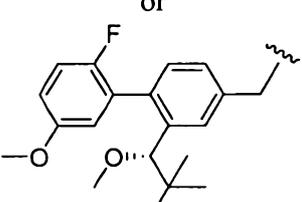
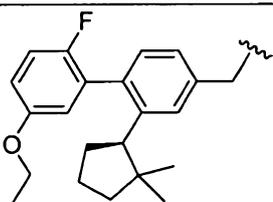
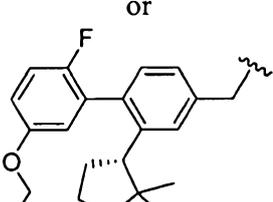
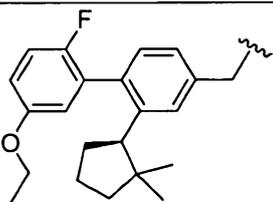
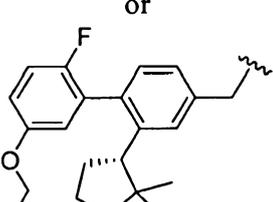
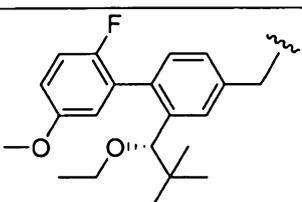
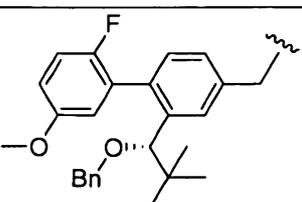
Table 6



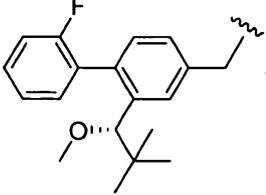
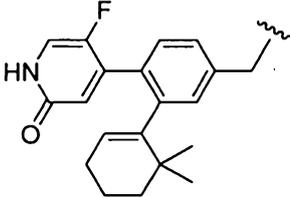
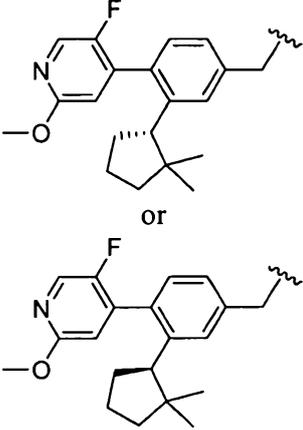
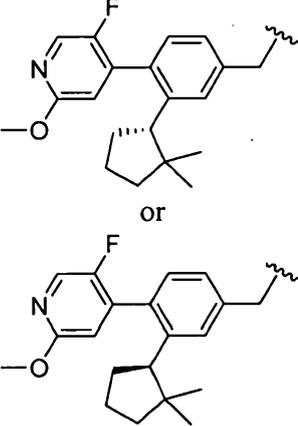
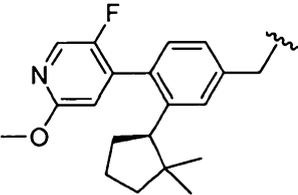
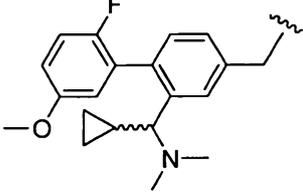
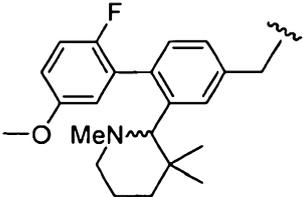
Compound	TG	Compound	TG
66.1		66.2	
66.3		66.4	
66.5	 or 	66.6	 or but not the same one as 66.5

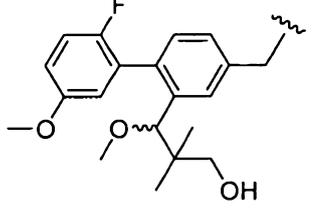
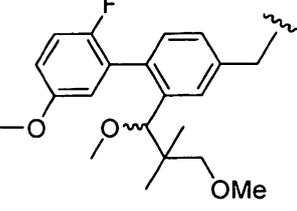
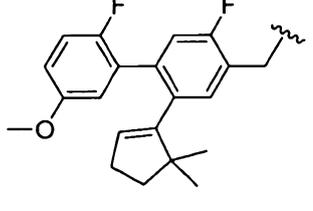
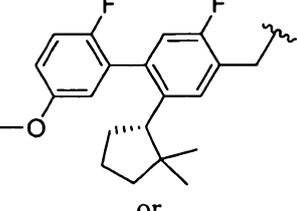
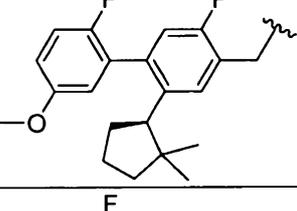
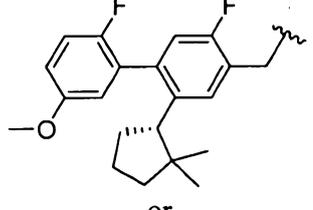
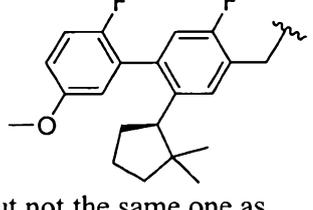
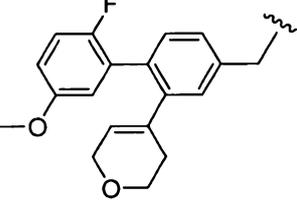
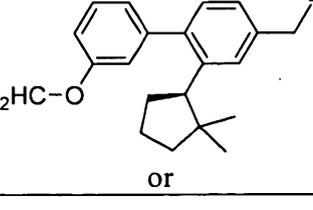
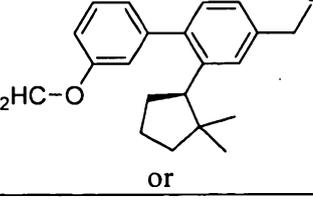
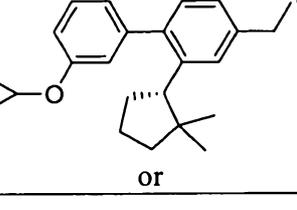
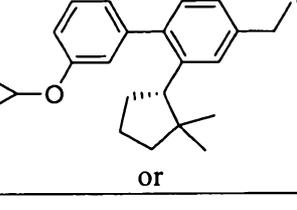
Compound	TG	Compound	TG
66.7	 <p style="text-align: center;">or</p>	66.8	 <p style="text-align: center;">or</p> <p>but not the same one as 66.7</p>
66.9		66.10	
66.11	 <p style="text-align: center;">or</p>	66.12	
66.13	 <p style="text-align: center;">or</p>	66.14	

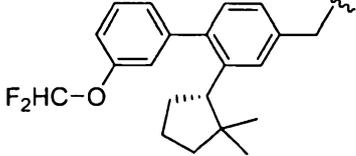
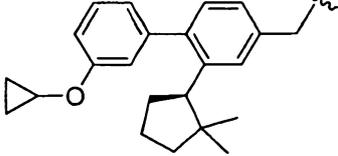
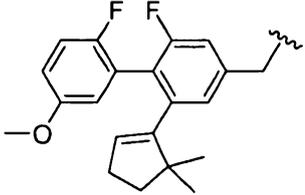
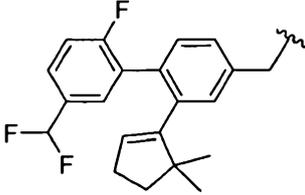
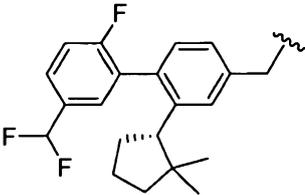
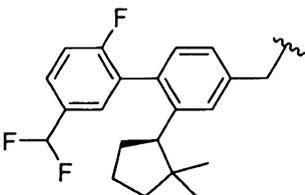
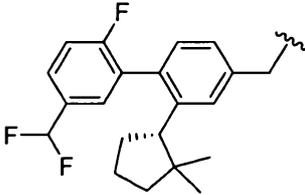
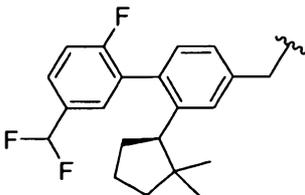
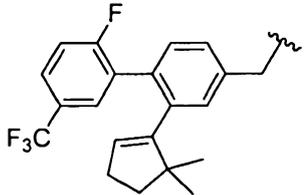
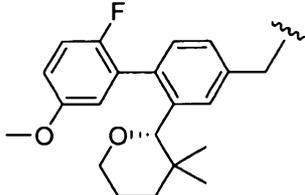
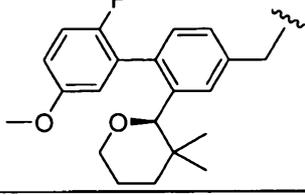
Compound	TG	Compound	TG
66.15		66.16	
66.17		66.18	 or 
66.19	 or  but not the same one as 66.18	66.20	
66.21	 or	66.22	 or

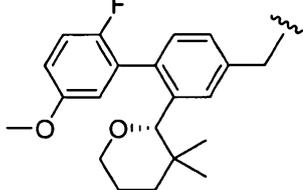
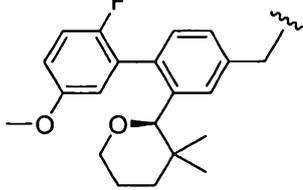
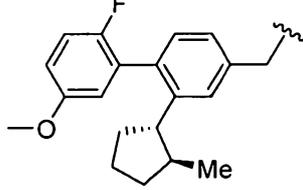
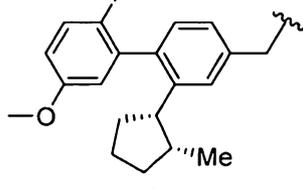
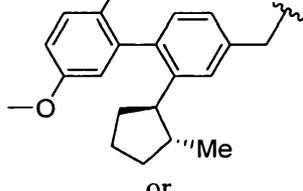
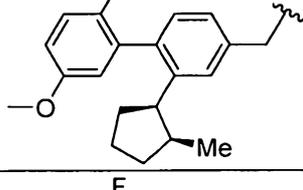
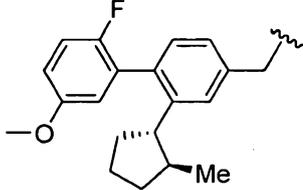
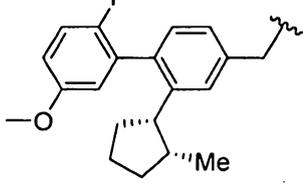
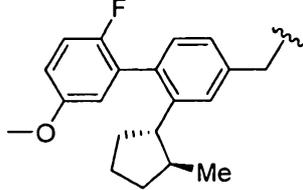
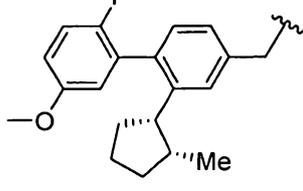
Compound	TG	Compound	TG
			 but not the same one as 66.21
66.23	 or 	66.24	 or  but not the same one as 66.13
66.25	 or 	66.26	 or  but not the same one as 66.25
66.27	 or 	66.28	 or 

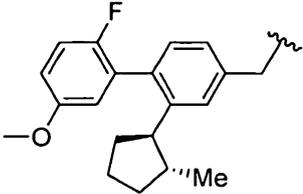
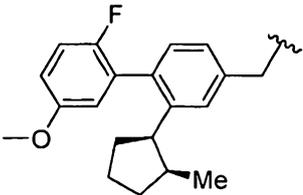
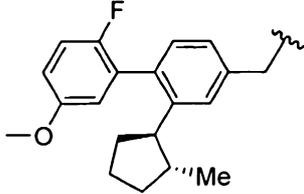
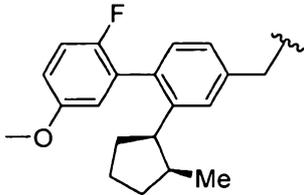
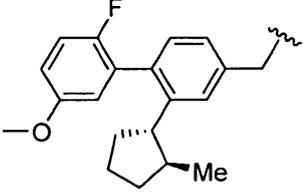
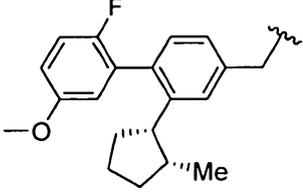
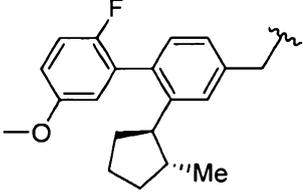
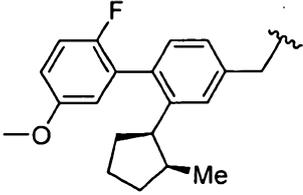
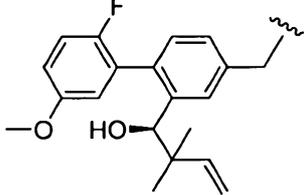
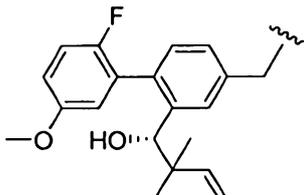
Compound	TG	Compound	TG
			 Bn = benzyl
66.29	 or 	66.30	 or
66.31	 or but not the same one as 66.30	66.32	 or
66.33	 or 	66.34	

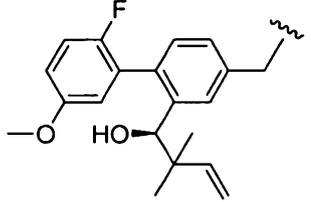
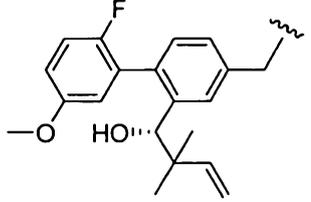
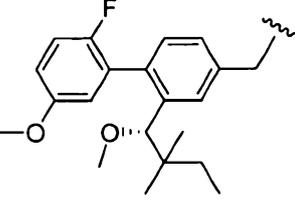
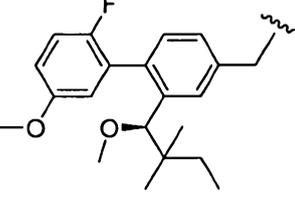
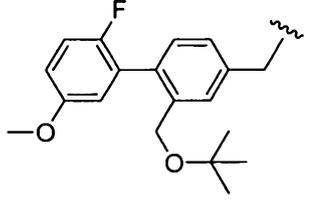
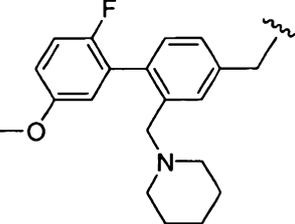
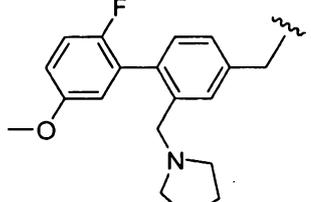
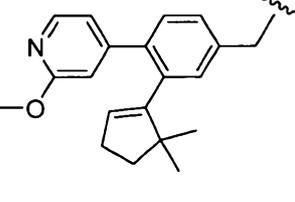
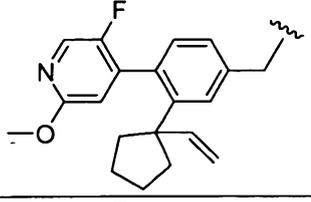
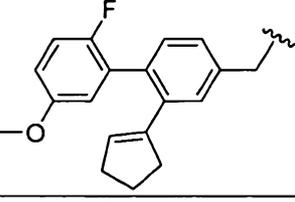
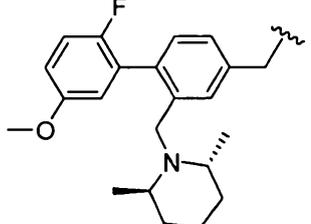
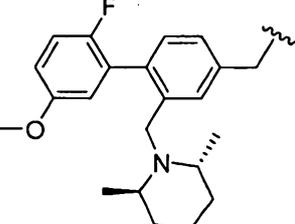
Compound	TG	Compound	TG
	 <p data-bbox="485 591 775 651">but not the same one as 66.32</p>		
66.35		66.36	 <p data-bbox="1193 869 1235 898">or</p>
66.37	 <p data-bbox="651 1346 692 1375">or</p>  <p data-bbox="485 1576 775 1637">but not the same one as 66.36</p>	66.38	
66.39	No compound associated with this number	66.40	

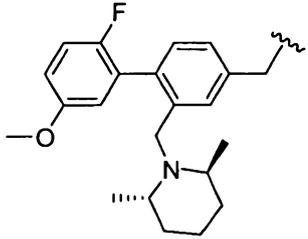
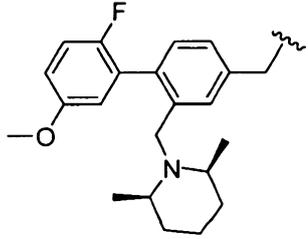
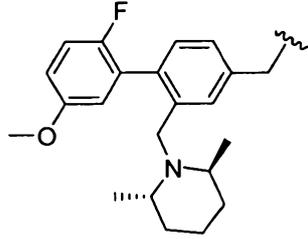
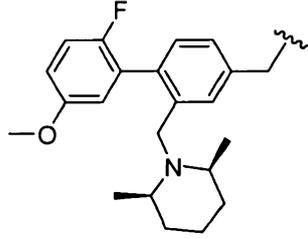
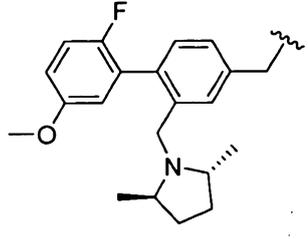
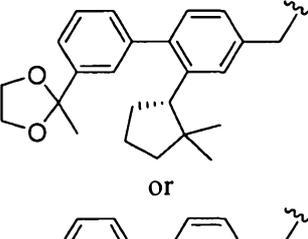
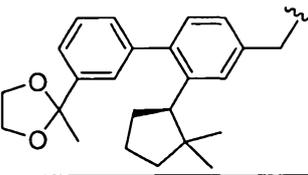
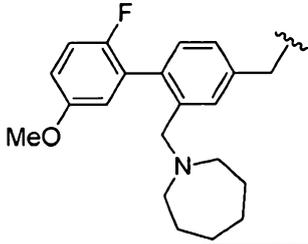
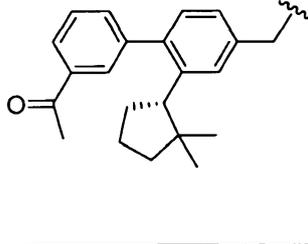
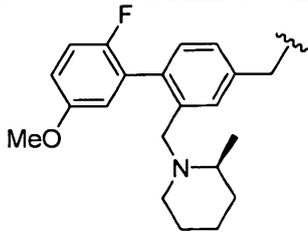
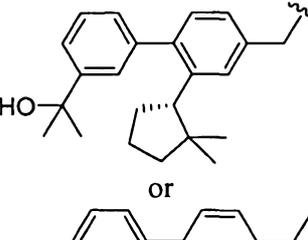
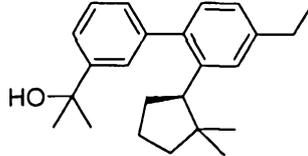
Compound	TG	Compound	TG
66.41		66.42	
66.43		66.44	 or 
66.45	 or  but not the same one as 66.44	66.46	
66.47	 or 	66.48	 or 

Compound	TG	Compound	TG
	 <p>but not the same one as 66.11</p>		
66.49		66.50	
66.51	 <p>or</p> 	66.52	 <p>or</p>  <p>but not the same one as 66.51</p>
66.53		66.54	 <p>or</p> 

Compound	TG	Compound	TG
<p>66.55</p>	 <p>or</p>  <p>but not the same one as 66.54</p>	<p>66.56</p>	 <p>or</p>  <p>or</p>  <p>or</p> 
<p>66.57</p>	 <p>or</p> 	<p>66.58</p>	 <p>or</p> 

Compound	TG	Compound	TG
	 <p>or</p>  <p>but not the same one as 66.56</p>		 <p>or</p>  <p>but not the same one as 66.56 or 66.57</p>
66.59	 <p>or</p>  <p>or</p>  <p>or</p>  <p>but not the same one as 66.56, 66.57, or 66.58</p>	66.60	 <p>or</p> 

Compound	TG	Compound	TG
66.61	 <p>or</p>  <p>but not the same one as 66.60</p>	66.62	 <p>or</p> 
66.63		66.64	
66.65		66.66	
66.67		66.68	
66.69	 <p>and</p>	66.70	 <p>and</p>

Compound	TG	Compound	TG
	 <p>or</p> 		 <p>or</p>  <p>but not the same as 66.69</p>
66.71		66.72	 <p>or</p> 
66.73		66.74	
66.75		66.76	 <p>or</p> 

Compound	TG	Compound	TG
66.77			

[0522] (3S)-3-(3-(((2-(Butyloxy)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclopropylpropanoic acid or (3R)-3-(3-(((2-(butyloxy)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclopropylpropanoic acid (66.1). MS ESI (neg.) m/e: 473.2 (M-H).

[0523] (3S)-3-(3-(((2-Cycloheptyl-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclopropylpropanoic acid or (3R)-3-(3-(((2-cycloheptyl-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclopropylpropanoic acid (66.2). MS ESI (neg.) m/e: 515.2 (M-H)⁺.

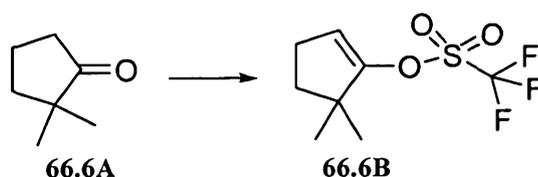
[0524] (3S)-3-Cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.3). MS ESI (neg.) m/e: 991.5 (2M-H)⁺, 495.2 (M-H)⁺.

[0525] (3S)-3-Cyclopropyl-3-(3-(((2-(2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-(2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.4). MS ESI (neg.) m/e: 515.3 (M-H).

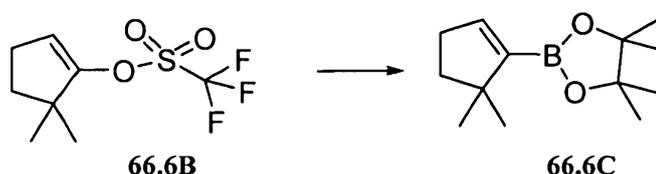
[0526] (3S)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-

((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.5). MS ESI (neg.) m/e: 515.3 (M-H)⁺.

[0527] **Example 66.6**

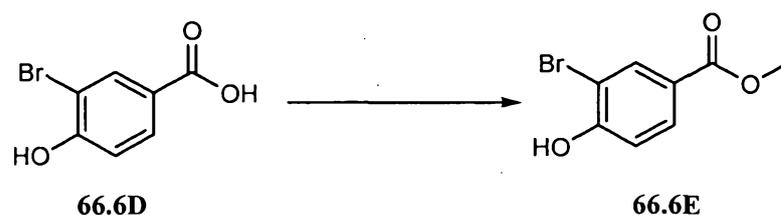


[0528] **5,5-Dimethylcyclopent-1-enyl trifluoromethanesulfonate (66.6B).** To a solution of 2,2-dimethylcyclopentanone **66.6A** (available from ChemSampCo)(3.00 g, 26.75 mmol) in THF (100 mL), was slowly added LDA (14.7 mL, 2.0 M, in heptane) at -78°C. The resulting mixture was stirred at -78°C for 1 hour. A solution of N-phenyltriflimide (10.00 g, 28.00 mmol) was added to the mixture at -78 °C, and stirring was continued at 0°C for 2 hours and then at room temperature overnight. The reaction mixture was extracted with hexane (80× 2 mL). The organic layer was washed with saturated Na₂CO₃ (30 mL), brine (20 mL), and dried with MgSO₄. The solvent was removed, and the crude product was purified by CombiFlash (eluant was EtOAc and hexane) to give **66.6B**. ¹H NMR (CDCl₃) δ ppm 1.16 (s, 6 H), 1.86 (t, J = 7.1 Hz, 2 H), 2.36 (t, J = 7.1 Hz, 2 H), 5.56 (m, 1 H).

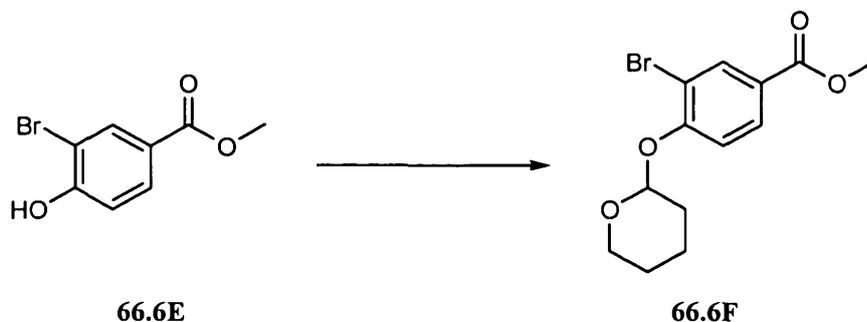


[0529] **2-(5,5-Dimethylcyclopent-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (66.6C).** KOPh was prepared by dissolving commercially available phenol (100 g, 1063 mmol) in MeOH (300 mL) and then adding a mixture of potassium hydroxide (20 mL, 1052 mmol) dissolved in MeOH (80 mL) and water (80 mL). The resulting solution was mixed well and flushed with nitrogen. The solvent was then removed by rotary evaporator at 50-60°C. The resulting product was ground to fine powders and pumped on at high vacuum at 60°C for 1 hour to give KOPh as an off white solid. PdCl₂(PPh₃)₂ (0.56 g, 0.80 mmol), PPh₃ (0.63 g, 2.40 mmol),

bis(pinacolato)diboron (6.80 g, 26.75 mmol) and KOPh (fine powder, 5.30 g, 40.10 mmol) were added to a flask. The flask was flushed with nitrogen and charged with toluene (100 mL) and with **66.6B** (6.53 g, 26.75 mmol). The mixture was stirred at 50 °C for 2 hours. The reaction mixture was treated with water at room temperature and extracted with benzene (60× 2 mL). The organic layer was dried over MgSO₄. The product was then purified by CombiFlash to give intermediate **66.6C**. ¹H NMR (CDCl₃) δ ppm 1.04 (s, 6 H), 1.18 (s, 12 H), 1.57 (t, J = 7.1 Hz, 2 H), 2.29 (t, J = 7.1 Hz, 2 H), 6.29 (m, 1 H).

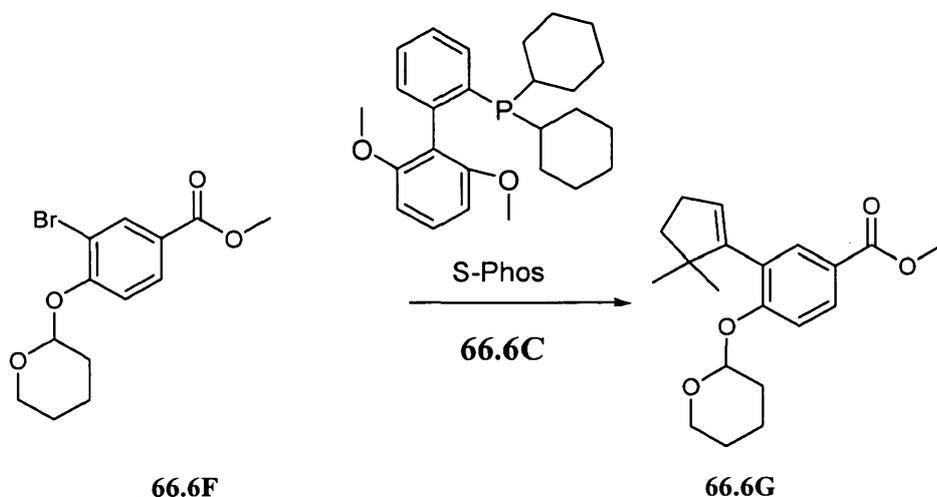


[0530] Methyl 3-bromo-4-hydroxybenzoate (66.6E). To a stirred solution of 3-bromo-4-hydroxybenzoic acid (**66.6D**) (available from Alfa Aesar, Avocado, Lancaster) (50.0 g, 231 mmol) in MeOH (300 mL) was added a cold solution of sulfuric acid (2.50 mL, 47 mmol). The mixture was heated to 80°C and monitored by TLC. After 16.5 hours, the solvent was removed and the reaction mixture was diluted with EtOAc. The organic phase was washed carefully two times with saturated aqueous NaHCO₃, once with brine, and then dried over anhydrous sodium sulfate. After filtration, the organic solvent was removed in vacuo to yield **66.6E** as a white solid (yield 100%) that was used without purification.



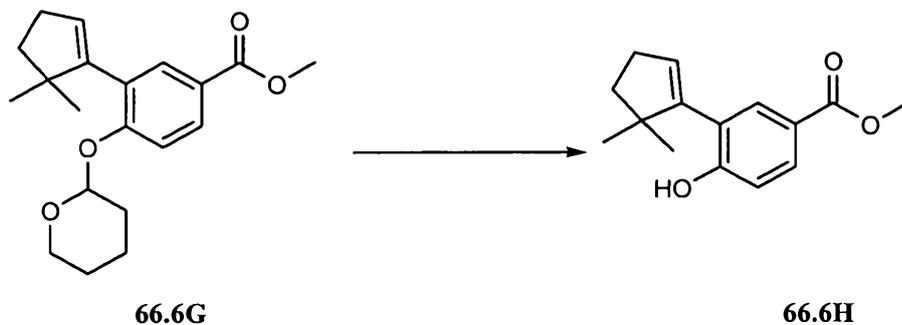
[0531] Methyl 3-bromo-4-(tetrahydro-2H-pyran-2-yloxy)benzoate (66.6F). To a stirred solution of **66.6E** (38 g, 164 mmol) and 3,4-dihydro-2H-pyran (45 mL, 493 mmol) in DCM (355 mL,) was added 4-methylbenzenesulfonic acid hydrate (0.63 g, 3.30

mmol). The mixture was stirred at room temperature and monitored by TLC. After 2 hours, the solution was washed with a mixed aqueous solution of saturated aqueous sodium bicarbonate/brine/water (1:1:2). The aqueous layer was extracted three times with ether. After drying over anhydrous sodium sulfate and then filtering, the organic solvent was removed under reduced pressure. The crude material was purified on silica gel (0-10% EtOAc in hexanes) to yield a white solid. The product was recrystallized from MeOH to provide **66.6F** (yield 90%). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.24 (1 H, d, J=2.0 Hz), 7.93 (1 H, dd, J=8.6, 2.0 Hz), 7.17 (1 H, d, J=8.6 Hz), 5.62 (1 H, t, J=2.5 Hz), 3.90 (3 H, s), 3.83 (1 H, td, J=11.1, 2.9 Hz), 3.66 (1 H, m), 2.18 (1 H, m), 2.04 (1 H, m), 1.94 (1 H, m), 1.79 (2 H, m), 1.67 (1 H, m).



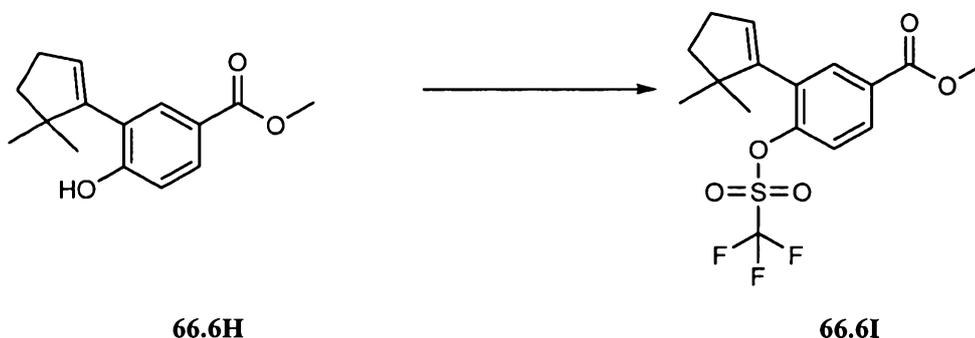
[0532] **Methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-(tetrahydro-2H-pyran-2-yloxy)benzoate (66.6G)**. A stirred mixture of **66.6F** (10.1 g, 31.9 mmol), grounded S-Phos (2.62 g, 6.39 mmol), palladium acetate (0.72 g, 3.2 mmol), and potassium phosphate, tribasic (17.0 g, 80.2 mmol) in DMF (70 mL) and water (3.5 mL) was purged three times with argon and placed under vacuum three times. Before heating, 2-(5,5-dimethylcyclopent-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**66.6C**) (8.50 g, 38.3 mmol) was added via syringe. The resulting mixture was then heated to 75°C. After 21 hours (black solution), the reaction was cooled to room temperature, diluted with water, and extracted three times with EtOAc. The organic layers were combined and washed twice with brine. After drying over anhydrous sodium sulfate and filtering, the organic solvent was removed under reduced pressure. The residue was purified on silica gel (0-20% EtOAc in hexanes) to yield **66.6G** as a colorless oil that solidified (yield 80%). ¹H

NMR (400 MHz) (CDCl₃) δ ppm 7.91 (1 H, dd, J=8.6, 2.3 Hz), 7.74 (1 H, d, J=2.3 Hz), 7.15 (1 H, d, J=8.6 Hz), 5.55 (1 H, t, J=2.3 Hz), 5.49 (1 H, t, J=2.9 Hz), 3.88 (3 H, s), 3.82 (1 H, td, J=11.1, 2.9 Hz), 3.64 (1 H, m), 2.43 (2 H, td, J=7.0, 2.3 Hz), 1.92 (5 H, m), 1.69 (1 H, m), 1.61 (2 H, m), 1.09 (6 H, d, J=13.7 Hz).



[0533] Methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-hydroxybenzoate (66.6H).

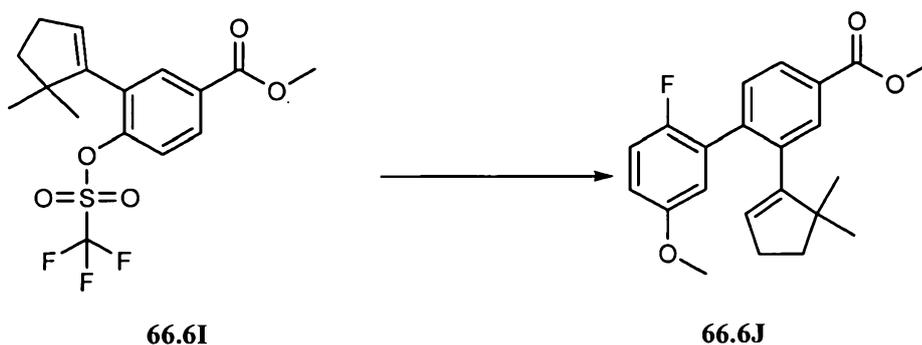
To a stirred solution of **66.6G** (19.0 g, 57.6 mmol) in MeOH (150 mL) was added PPTS (1.46 g, 5.80 mmol). The mixture was heated to 50°C and monitored with TLC. After 19 hours, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-15% EtOAc in hexanes) to yield **66.6H** as a white solid (yield 90%). ¹H NMR (400 MHz) (CDCl₃) δ ppm 7.89 (1 H, dd, J=8.6, 2.0 Hz), 7.79 (1 H, d, J=2.3 Hz), 6.97 (1 H, d, J=8.6 Hz), 5.87 (1 H, s), 5.81 (1 H, t, J=2.3 Hz), 3.89 (3 H, s), 2.51 (2 H, td, J=7.1, 2.5 Hz), 1.94 (2 H, t, J=7.0 Hz), 1.12 (6 H, s).



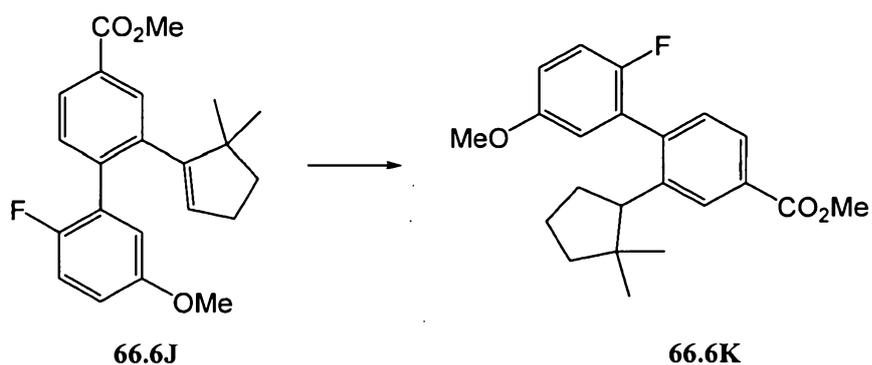
[0534] Methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-

(trifluoromethylsulfonyloxy)benzoate (66.6I). To a stirred solution of **66.6H** (6.00 g, 24.4 mmol) in dry DCM (35 mL) was added TEA (6.80 mL, 48.9 mmol) and 4-dimethylaminopyridine (0.30 g, 2.5 mmol). After about 20 minutes, N-phenyl bis-trifluoromethane sulfonimide (10.5 g, 29.3 mmol) was added in portion. Upon complete

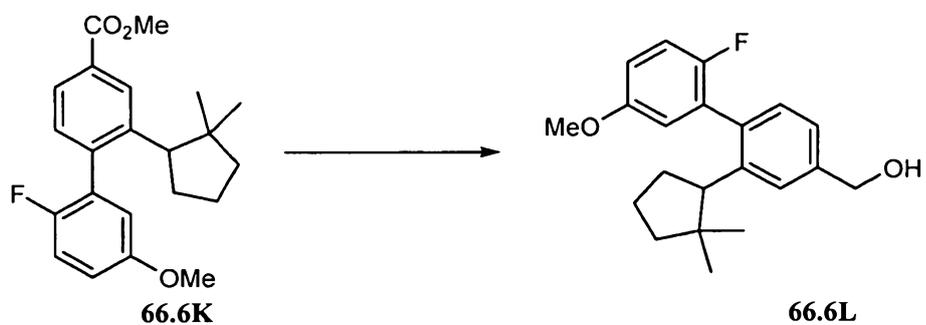
addition, the solution was stirred at room temperature and monitored with TLC. After 3 hours, the reaction was diluted with brine and extracted three times with DCM. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.6I** as a colorless oil (yield 88%). ^1H NMR (400 MHz, CDCl_3) δ ppm 8.02 (1 H, dd, $J=8.6, 2.0$ Hz), 7.94 (1 H, d, $J=2.0$ Hz), 7.35 (1 H, d, $J=8.6$ Hz), 5.80 (1 H, t, $J=2.5$ Hz), 3.94 (3 H, s), 2.48 (2 H, td, $J=7.0, 2.3$ Hz), 1.91 (2 H, t, $J=7.0$ Hz), 1.09 (6 H, s).

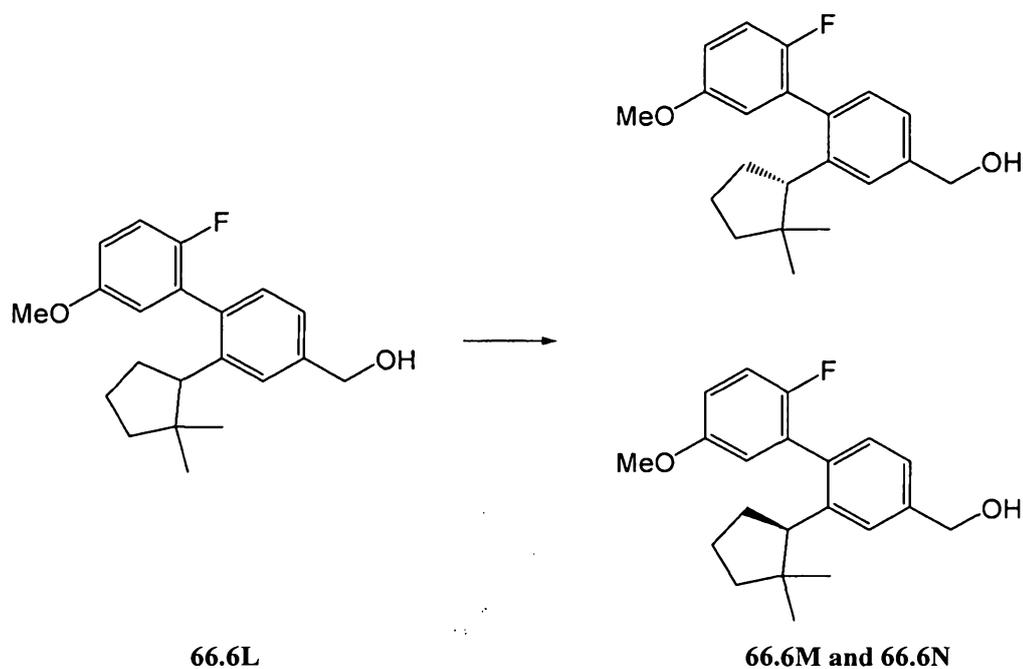


[0535] Synthesis of 66.6J. To a stirred solution of **66.6I** (8.71 g, 23.0 mmol) in DMF (20 mL) at 23°C was added 2-fluoro-5-methoxyphenylboronic acid (7.84 g, 46.1 mmol) and potassium carbonate (9.56 g, 69.1 mmol) followed by tetrakis(triphenylphosphine)palladium (0) (2.67 g, 2.31 mmol). The mixture was heated to 90°C. After 15 hours, LCMS showed that the reaction was complete. The mixture was then cooled to room temperature and then diluted with water. After extracting three times with EtOAc, the mixture was concentrated in vacuo and then purified on silica gel (0%-10% EtOAc/hexane) to give **66.6J** as a clear oil that solidified (yield 91%). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.98 (1 H, dd, $J=8.0, 1.8$ Hz), 7.91 (1 H, d, $J=2.0$ Hz), 7.40 (1 H, d, $J=7.8$ Hz), 6.98 (1 H, t, $J=8.8$ Hz), 6.85 (2 H, m), 5.55 (1 H, s), 3.95 (3 H, s), 3.77 (3 H, s), 2.27 (2 H, td, $J=7.0, 2.7$ Hz), 1.68 (2 H, t, $J=7.0$ Hz), 0.87 (6 H, s).



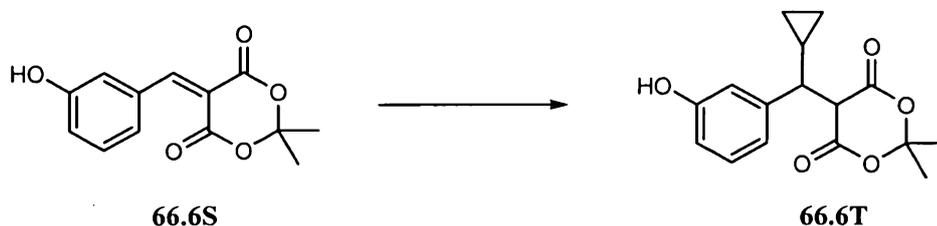
[0536] **Synthesis of 66.6K.** To a stirred solution of **66.6J** (0.660 g, 1.86 mmol) in MeOH (20.00 mL, 1.86 mmol) at 23°C was added Pd/C (0.0198 g, 0.186 mmol). The reaction was stirred under an atmosphere of hydrogen (0.00375 g, 1.86 mmol) for 16 hours. The reaction mixture was then filtered and concentrated in vacuo to give **66.6K** as a clear oil (0.600 g, 90.4% yield).



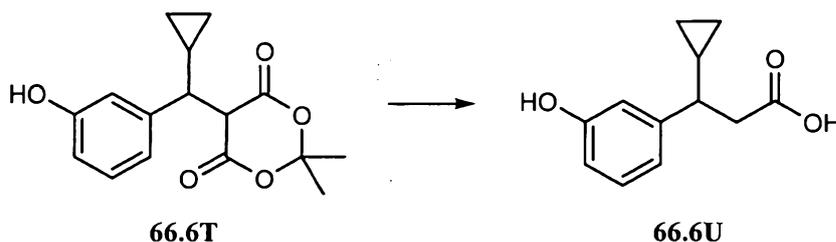


[0537] **Synthesis of 66.6L, 66.6M, and 66.6N.** To a stirred solution of **66.6K** (0.500 g, 1.4 mmol) in THF (7.0 mL, 1.4 mmol) at 0°C was added LAH (1.4 mL, 1.4 mmol). After addition, the reaction was stirred for 1.5 hours. 1N NaOH (aq) was then added to quench the reaction, and the mixture was then extracted with EtOAc. The organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. The resulting product was then purified on silica gel (0%-20% EtOAc/hexane) to give **66.6L** (0.442 g, 96% yield). Chiral separation of **66.6L** was accomplished on Chiracel-OD (3%IPA in hexane) to provide **66.6M** and **66.6N**. Both enantiomers were used to synthesize example compounds, and both enantiomers gave active example compounds. However, the enantiomer corresponding to peak 2 provided the most active example compounds. Analytical column (Chiracel-OD (2%IPA in hexane, 45 min run) Peak 1-15.5 mins, Peak 2-38.0 mins).¹

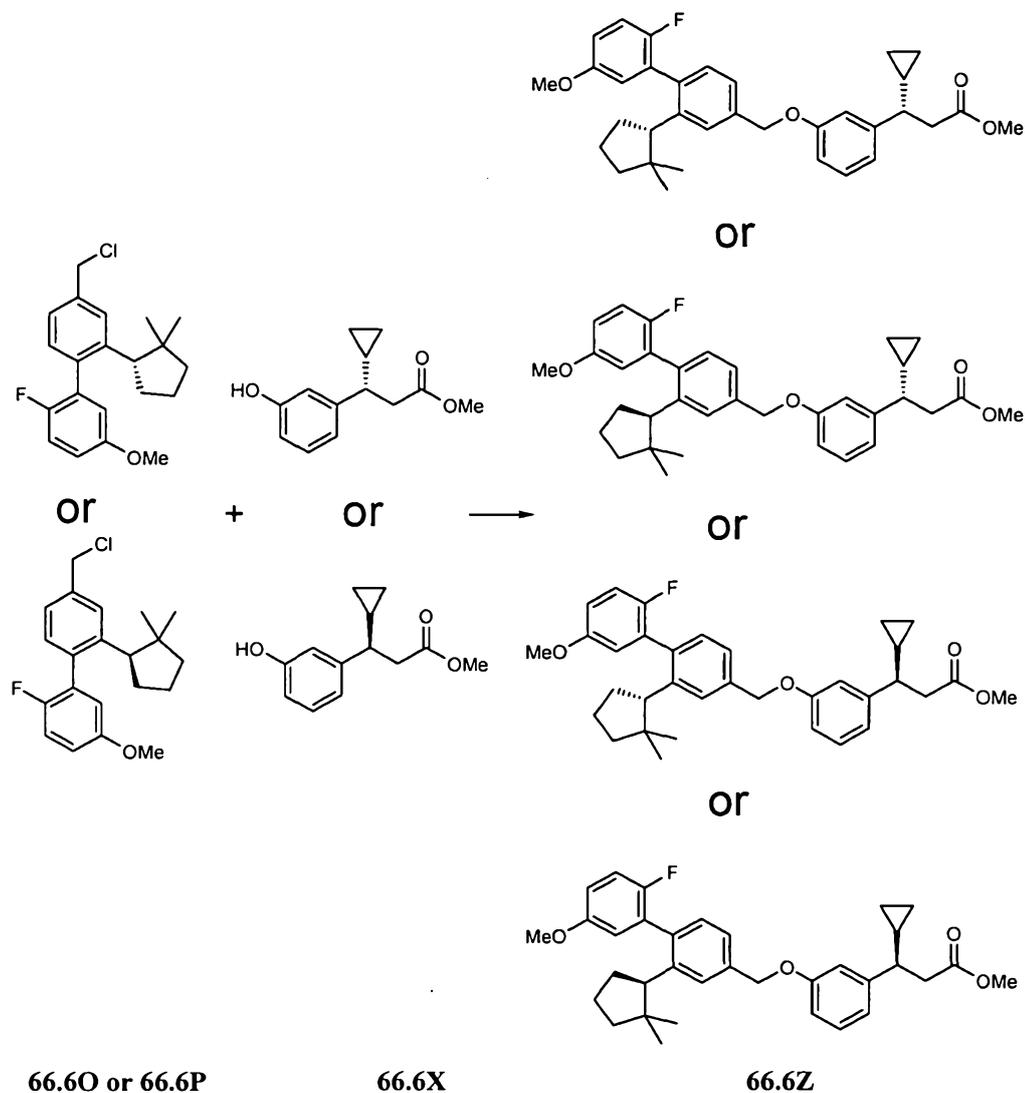
5-(3-hydroxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione **66.6S** (41.4 g, 83% yield) as a yellow solid.



[0540] **5-(Cyclopropyl(3-hydroxyphenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (66.6T)**. To a solution of 5-(3-hydroxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione **66.6S** (2.00 g, 8.06 mmol) in THF (25 mL) was added cyclopropylmagnesium bromide (available from Aldrich)(0.5M, 96.7 mL, 48.3 mmol) via cannula at 0°C. The resulting heterogeneous mixture was warmed to room temperature, stirred for 30 minutes, and quenched with 1 N aqueous HCl. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel flash chromatography (10-35% EtOAc/hexane) to afford 5-(cyclopropyl(3-hydroxyphenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione **66.6T** (2.04 g, 87% yield) as a yellow oil.

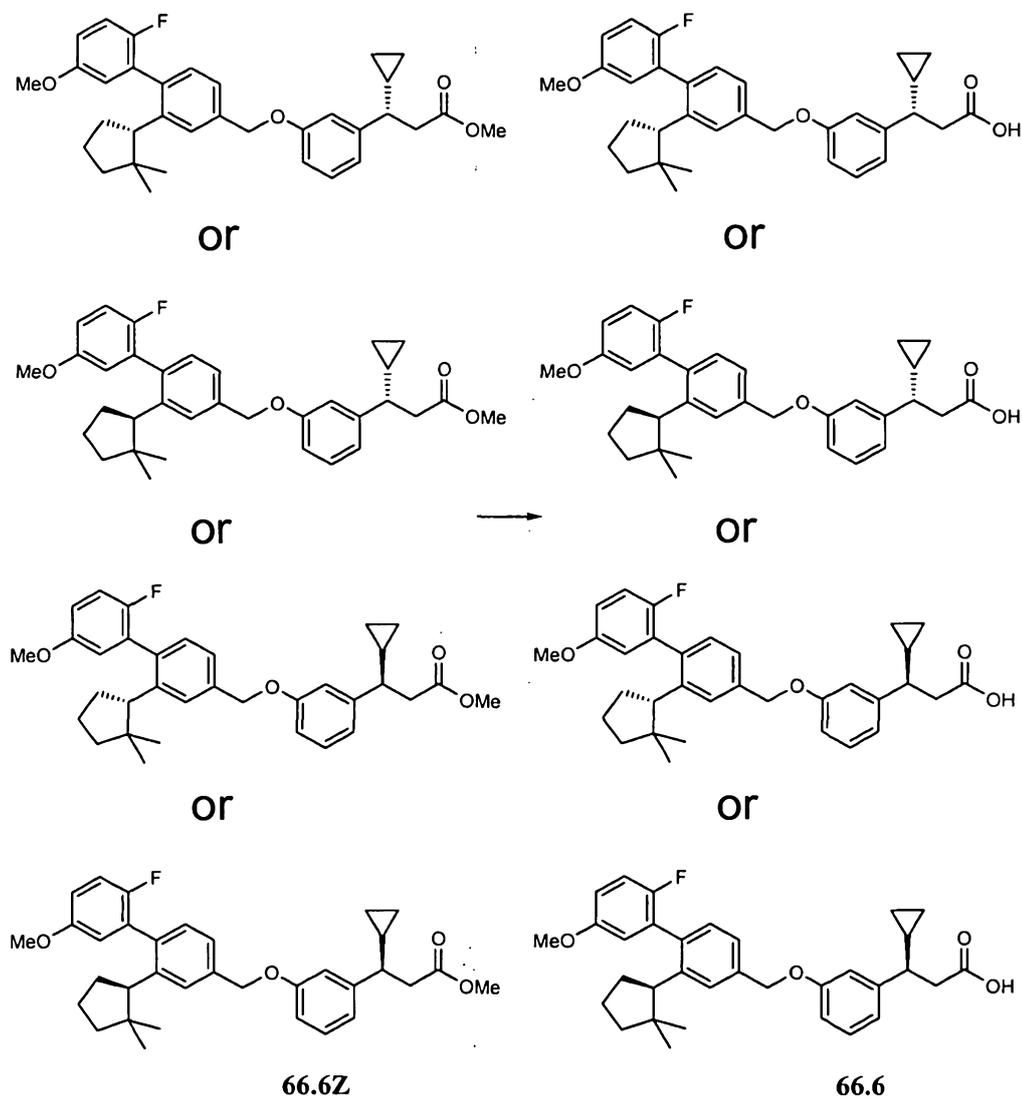


[0541] **3-Cyclopropyl-3-(3-hydroxyphenyl)propanoic acid (66.6U)**. 5-(Cyclopropyl(3-hydroxyphenyl)methyl)-2,2-dimethyl-1,3-dioxane-4,6-dione **66.6T** (14.64 g, 50.43 mmol) in DMF/water (10/1) (220 mL) was heated at 90°C overnight. The reaction was then diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated to give **66.6U** as a clear oil (10.40g, 100%).



[0543] **Methyl (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3S)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.6Z).** To a stirred solution of **66.6X** (0.350 g, 1.59 mmol) in DMF (20.00 mL, 1.59 mmol) at 23°C was added **66.6O** or **66.6P** (0.551 g, 1.59 mmol) followed by cesium carbonate (1.04 g, 3.18 mmol). The resulting mixture

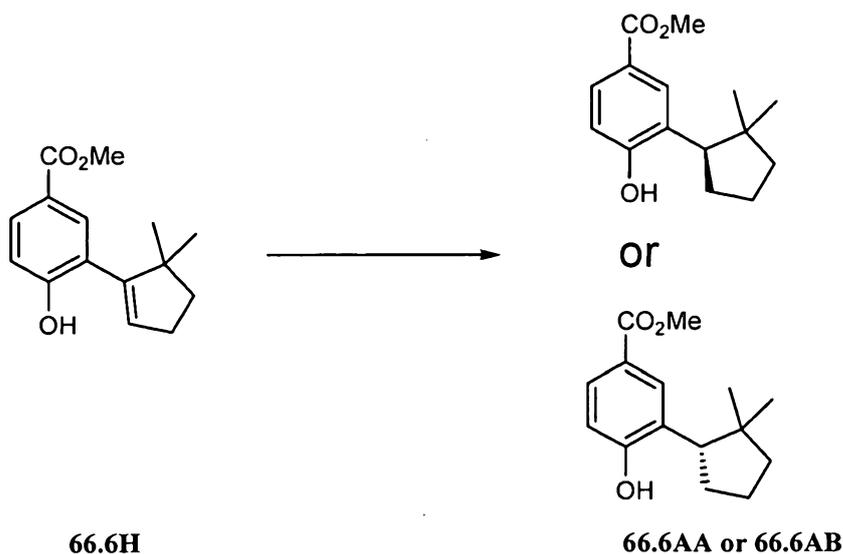
was stirred for 20 hours. Water was then added to the reaction, and the resulting mixture was extracted with EtOAc. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified on silica gel (0%-20% EtOAc/hexane) to give Product **66.6Z** (0.843 g, 100.0% yield).



[0544] (3S)-3-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-

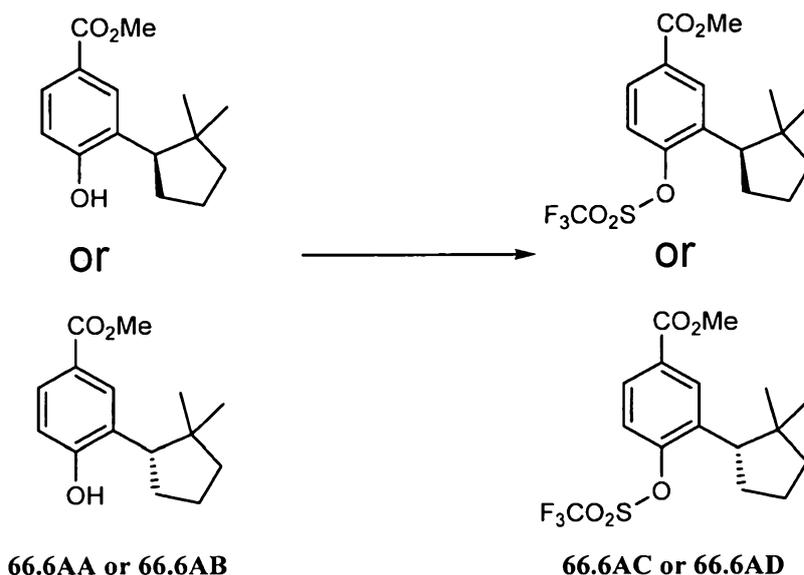
yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.6). To a stirred solution of 66.6Z (0.843 g, 1.6 mmol) in THF (25.00 mL, 305 mmol) and EtOH (25.00 mL, 1.6 mmol) at 23°C was added LiOH (1.6 mL, 1.6 mmol). The mixture was stirred at 23°C for 16 hours. The reaction mixture was concentrated in vacuo. 1N HCl was then added to the mixture, and the resulting mixture was extracted with EtOAc. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified on silica gel (0%-30% EtOAc/hexane) to give 66.6 (0.7422 g, 90% yield). MS ESI (neg.) m/e: 515.2 (M-H)⁺. Compound 66.5 is a diastereomer of 66.6 because the same head group was used to synthesize it that was used to prepare 66.6, but the tail groups used were different.

[0545] **Asymmetric synthesis of 66.6O or 66.6P.** The following procedures were used to synthesize 66.6O or 66.6P using a highly enantioselective procedure to hydrogenate 66.6H to form 66.6AA or 66.6AB.

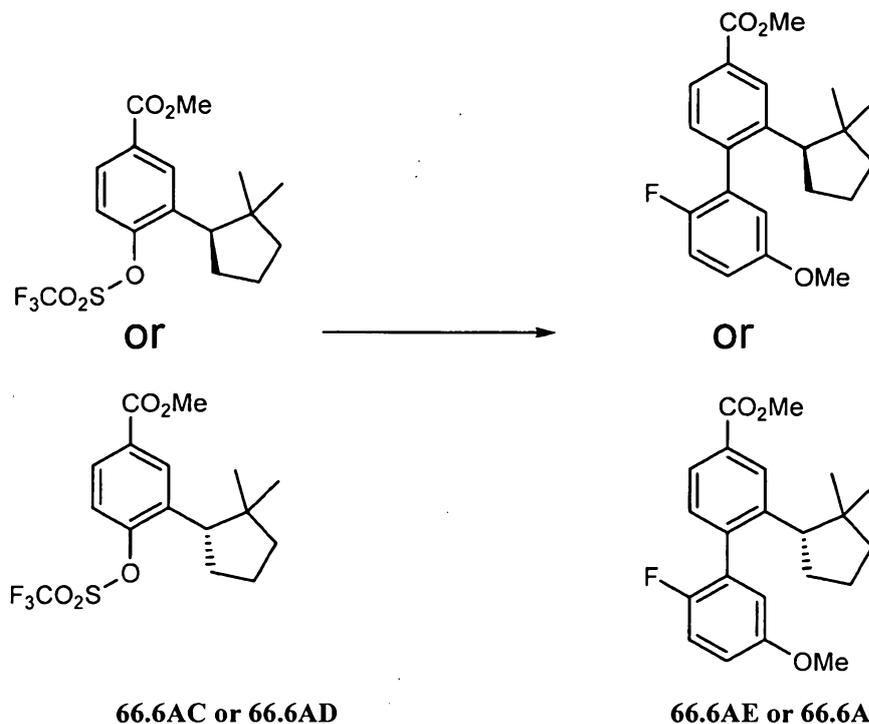


[0546] **(R)-methyl 3-(2,2-dimethylcyclopentyl)-4-hydroxybenzoate (66.6AA) or (S)-methyl 3-(2,2-dimethylcyclopentyl)-4-hydroxybenzoate (66.6AB).** A mixture of Rh(COD)₂BF₄ (Stern Chemical, 35138-22-8, 137.2 mg, 0.338 mmol) and (R)-1-[(S)-2-(R)-(ditertbutylphosphino)ferrocenyl]ethyl-bis-(3,5-bistrifluoromethylphenyl)phosphine (Solvias, SL-J210-1, 302 mg, 0.3718 mmol) was stirred in THF (300 mL) under N₂ for 60 minutes and a dark red solution formed. To the resulting solution was added methyl 3-

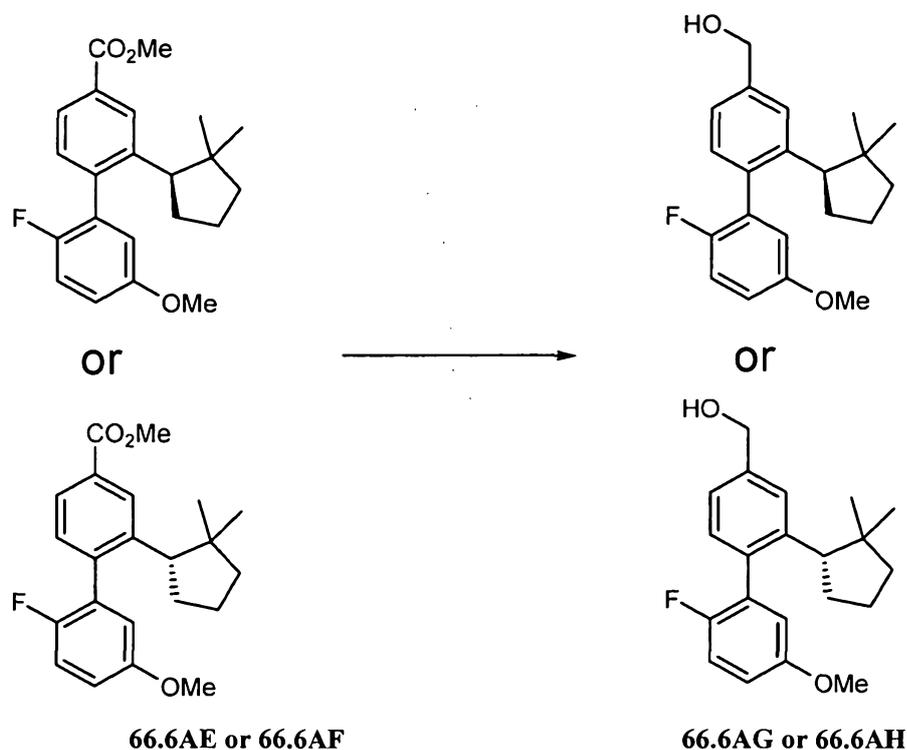
(5,5-dimethylcyclopent-1-enyl)-4-hydroxybenzoate **66.6H** (41.64g, 168.98 mmol) and TEA (10mol%, 2.35 mL, 16.9mmol). The resulting solution was filled with H₂ (200psi) three times and stirred at room temperature/200psi for 2 hours. The reaction mixture was then passed through a short plug of silica gel, eluting with 1:1 hexane/EtOAc, followed by concentration afforded the desired product as a white solid (98.9A% conversion, 99% yield (41.6 g), 99% ee).



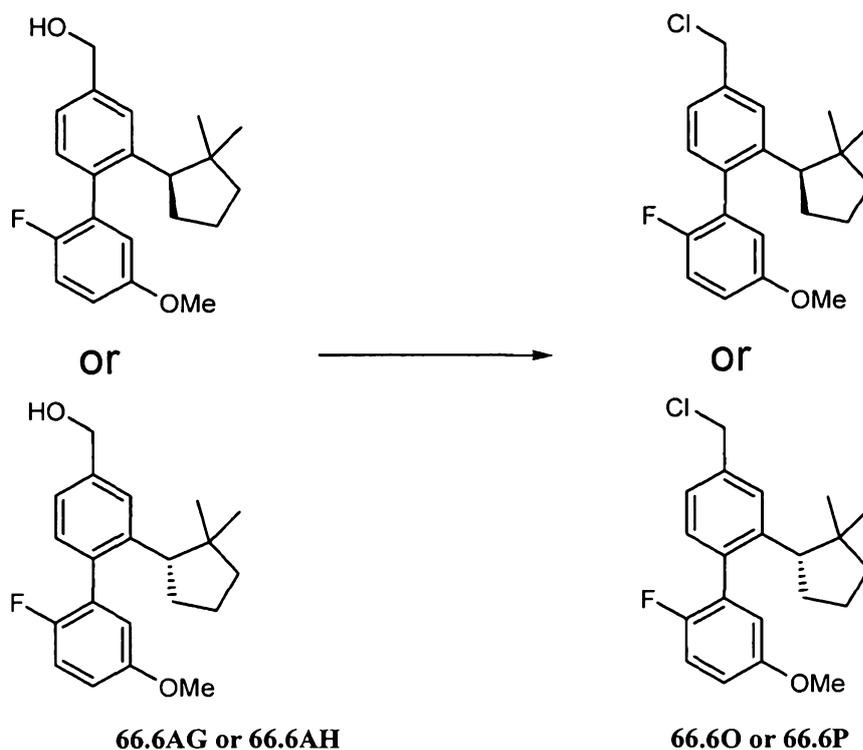
[0547] **(R)-methyl 3-(2,2-dimethylcyclopentyl)-4-(trifluoromethylsulfonyloxy)benzoate or (S)-methyl 3-(2,2-dimethylcyclopentyl)-4-(trifluoromethylsulfonyloxy)benzoate (66.6AC or 66.6AD).** To a stirred solution of (R)-methyl 3-(2,2-dimethylcyclopentyl)-4-hydroxybenzoate or (S)-methyl 3-(2,2-dimethylcyclopentyl)-4-hydroxybenzoate (**66.6AA or 66.6AB**) (18.00 g, 72 mmol) in DCM (181 mL, 72 mmol) at 23°C was added TEA (12 mL, 87 mmol) and a catalytic amount of DMAP. N-phenyltriflimide (28 g, 80 mmol) was then added to the mixture and stirring was continued at room temperature for 16 hours. The reaction was concentrated in vacuo. The residue was purified on silica gel (0-10% EtOAc in hexanes) to yield **66.6AC or 66.6AD** as a colorless oil (27.7 g, 100% yield). MS ESI (pos.) m/e: 381.1 (M+H)⁺.



[0548] **Methyl 2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate or methyl 2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.6AE or 66.6AF).** To a stirred solution of (S)-methyl 3-(2,2-dimethylcyclopentyl)-4-(trifluoromethylsulfonyloxy)benzoate or (R)-methyl 3-(2,2-dimethylcyclopentyl)-4-(trifluoromethylsulfonyloxy)benzoate (**66.6AC or 66.6AD**) (28.5 g, 75 mmol) in DMF (375 mL, 75 mmol) at 23°C was added 2-fluoro-5-methoxyphenylboronic acid (19 g, 112 mmol)(commercially available from Aldrich), potassium carbonate (31 g, 225 mmol), and then tetrakis(triphenylphosphine)palladium (4 g, 4 mmol). The mixture was heated to 90°C. Stirring was continued for 20 hours, after which, the reaction was cooled to room temperature, diluted with water, and extracted three times with EtOAc. The organic layers were combined and washed twice with brine. After drying over anhydrous sodium sulfate and filtering, the organic solvent was removed under reduced pressure. The residue was purified on silica gel (0-10% EtOAc in hexanes) to yield **66.6AE or 66.6AF** as a colorless oil (25.00 g, 94% yield). MS ESI (pos.) m/e: 357.1 (M+H)⁺.



[0549] (2-((1R)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol or (2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (**66.6AG or 66.6AF**). To a stirred solution of methyl 2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate or methyl 2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (**66.6AE or 66.6AF**) (29.50 g, 83 mmol) in THF (414 mL, 83 mmol) at 0°C was added LAH (124 mL, 124 mmol). Stirring was continued for 2 hours. Aqueous 1N NaOH was then added to quench the reaction, and the mixture was then extracted with EtOAc. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified on silica gel (0-20% EtOAc in hexanes) to yield **66.6AG or 66.6AH** as a colorless oil (23.66 g, 87% yield). MS ESI (pos.) m/e: 346.1 (M+H₂O)⁺.



[0550] **4-(Chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (66.6O or 66.6P).** To a stirred solution of (2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol or (2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (**66.6AG or 66.6AH**) (23.66 g, 72 mmol) in DCM (360 mL, 72 mmol) and DMF (0.56 mL, 7.2 mmol) at 0°C was added thionyl chloride (11 mL, 144 mmol). Stirring was continued at room temperature for 1 hour. The reaction was then concentrated in vacuo, and the residue was purified on silica gel (0-10% EtOAc in hexanes) to yield **66.6O** or **66.6P** as a colorless oil (23.0 g, 92% yield). MS ESI (pos.) m/e: 364.1 (M+H₂O)⁺.

[0551] **(3S)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-**

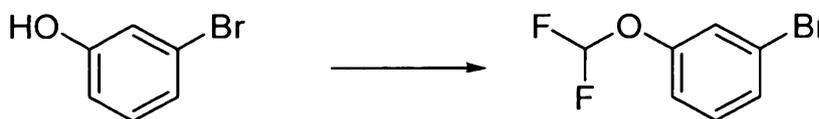
yl)methyl)oxy)phenyl)propanoic acid (66.7). MS ESI (neg.) m/e: 995.5 (2M-H)⁺, 497.3 (M-H)⁺.

[0552] **Diastereomer of 66.7 (66.8).** MS ESI (neg.) m/e: 995.5 (2M-H)⁺, 497.4 (M-H)⁺.

[0553] **(3S)-3-(3-(((2-Cycloheptyl-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclopropylpropanoic acid or (3R)-3-(3-(((2-cycloheptyl-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclopropylpropanoic acid (66.9).** MS ESI (neg.) m/e: 995.5 (2M-H)⁺, 497.3 (M-H)⁺.

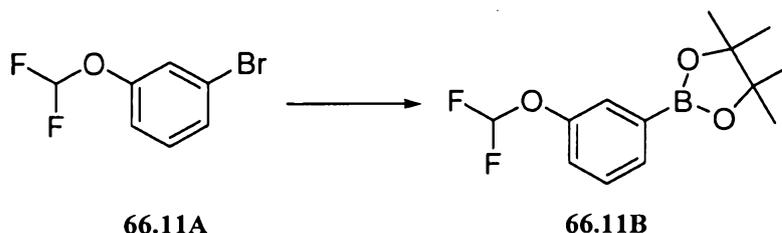
[0554] **(3S)-3-Cyclopropyl-3-(3-(((2-(6,6-dimethyl-1-cyclohexen-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-(6,6-dimethyl-1-cyclohexen-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.10).** MS ESI (neg.) m/e: 527.2 (M-H)⁺.

[0555] **Example 66.11**



66.11A

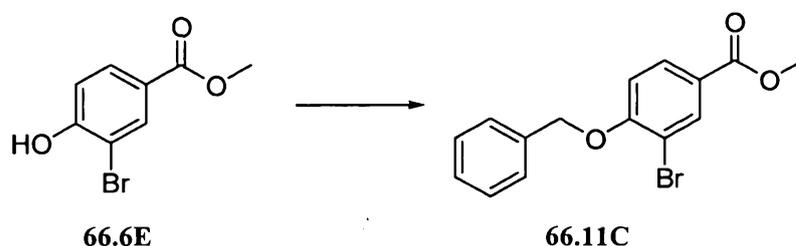
[0556] **1-Bromo-3-(difluoromethoxy)benzene (66.11A).** To a solution of 3-bromophenol (available from Sigma Aldrich) (1.28 g, 7.39 mmol) in DMF (12.0 mL) was added sodium 2-chloro-2,2-difluoroacetate (available from Sigma Aldrich) (2.82 g, 18.49 mmol) and cesium carbonate (4.82 g, 14.79 mmol). The reaction mixture was heated at 100°C. Gas was released from the reaction so care should be taken. After 2 hours, the reaction was cooled to room temperature then diluted with EtOAc, washed with water and then brine and re-extracted three times with EtOAc. The combined organic layers were dried over magnesium sulfate and then filtered, concentrated, and purified with silica gel chromatography (0-5% EtOAc in hexanes) to yield **66.11A** as an oil that was used without further purification (yield 61%).



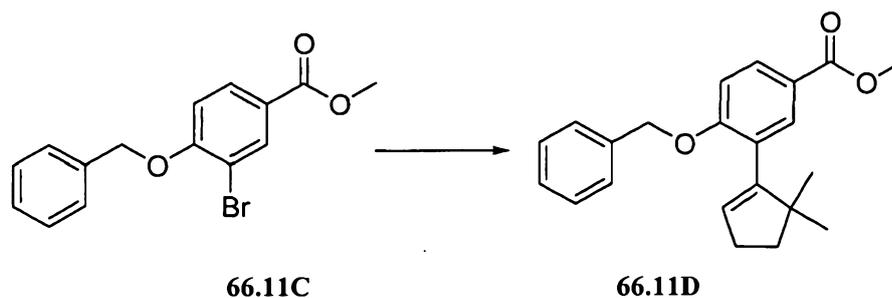
66.11A

66.11B

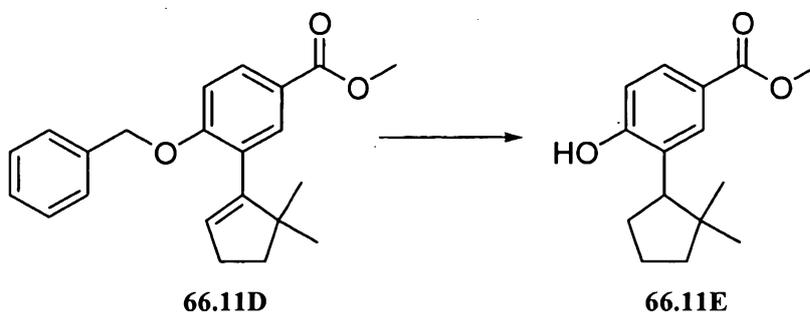
[0557] 2-(3-(Difluoromethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (66.11B). A stirred mixture of **66.11A** (1.00 g, 4.50 mmol), bis(pinacolato)diboron (1.26 g, 4.95 mmol), potassium acetate (1.34 g, 13.70 mmol), and dichloro[1,1'-bis(diphenylphosphino)ferrocene]dichloride palladium(II) DCM adduct (0.17 g, 0.23 mmol) in dry 1,4-dioxane (10.0 mL) was purged three times with argon and placed under vacuum three times. The mixture was heated to 100°C and monitored with LC-MS and TLC. After 21 hours, the reaction was cooled to room temperature and then filtered through Celite. The organic solvent was removed under reduced pressure, and the residue was purified on silica gel (0-10% EtOAc in hexanes) to yield **66.11B** as a colorless oil (0.41 g, 34%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.67 (1 H, d, J=7.4 Hz), 7.56 (1 H, d, J=2.3 Hz), 7.41 (1 H, m), 7.22 (1 H, dd, J=7.8, 2.3 Hz), 6.73 (1H, t, J= 74 Hz), 1.36 (12 H, s).



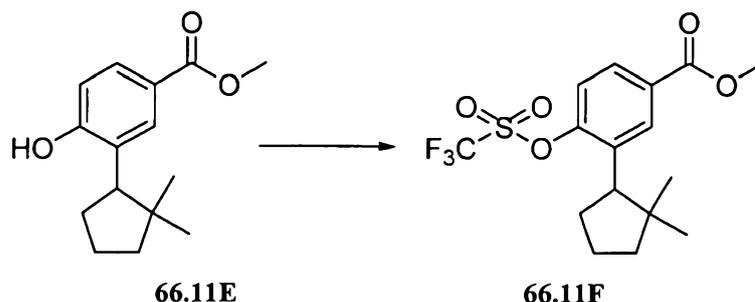
[0558] Methyl 4-(benzyloxy)-3-bromobenzoate (66.11C). To a solution of **66.6E** (53.2 g, 230 mmol) in DMSO (45.0 mL) was added 1-(bromomethyl)benzene (35.6 mL, 299 mmol). After cooling in an ice water bath, cesium carbonate (128 g, 391 mmol) was carefully added to the mixture, and the mixture was allowed to warm to room temperature. After overnight stirring, the mixture was diluted with water and extracted three times with EtOAc. The organic layers were combined and then washed with brine. After drying over anhydrous magnesium sulfate and filtration, the organic solvent was removed under reduced pressure to yield **66.11C** as a white solid.



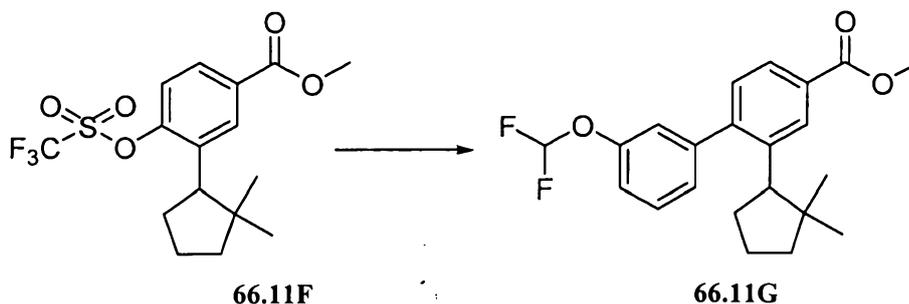
[0559] Methyl 4-(benzyloxy)-3-(5,5-dimethylcyclopent-1-enyl)benzoate (66.11D). A stirred mixture of **66.11C** (3.75 g, 11.66 mmol), ground S-Phos (0.96 g, 2.33 mmol), palladium acetate (0.26 g, 1.17 mmol), and potassium phosphate, tribasic (6.19 g, 29.17 mmol) in DMF (28.0 mL) and water (1.50 mL) was purged three times with argon and placed under vacuum three times. Before heating, 2-(5,5-dimethylcyclopent-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**66.6C**) (3.11 g, 13.99 mmol) was added via syringe, then the mixture was heated to 75 °C. After 21 hours (black solution), the reaction was cooled to room temperature, diluted with water, and extracted three times with EtOAc. The combined organic layers were washed twice with brine. After drying over anhydrous sodium sulfate and filtration, the organic solvent was removed under reduced pressure. The residue was purified on silica gel (0-10% EtOAc in hexanes) to yield **66.11D** as a colorless oil (3.03 g, 77%). MS ESI (pos.) m/e: 337.0 (M+H)⁺.



[0560] Methyl 3-(2,2-dimethylcyclopentyl)-4-hydroxybenzoate (66.11E). To a flask containing **66.11D** (3.03 g, 9.0 mmol) in MeOH (25.0 mL) was added palladium, 10% wt. on activated carbon (0.48 g, 0.45 mmol). After purging, the mixture was stirred under an atmosphere of hydrogen at room temperature. The reaction was monitored with TLC and LC-MS. After 27.5 hours, the reaction was filtered through Celite. After concentration, the residue was purified on silica gel using 0-50% EtOAc in hexanes to yield **66.11E** as a colorless oil that solidified (1.99 g, 89%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.91 (1 H, d, J=2.3 Hz), 7.79 (1 H, dd, J=8.4, 2.2 Hz), 6.82 (1 H, d, J=8.2 Hz), 5.54 (1 H, s), 3.90 (3 H, s), 3.17 (1 H, dd, J=10.4, 8.0 Hz), 2.17 (1 H, m), 2.04 (1 H, m), 1.92 (1 H, m), 1.81 (1 H, m), 1.68 (2 H, m), 1.06 (3 H, s), 0.72 (3 H, s).

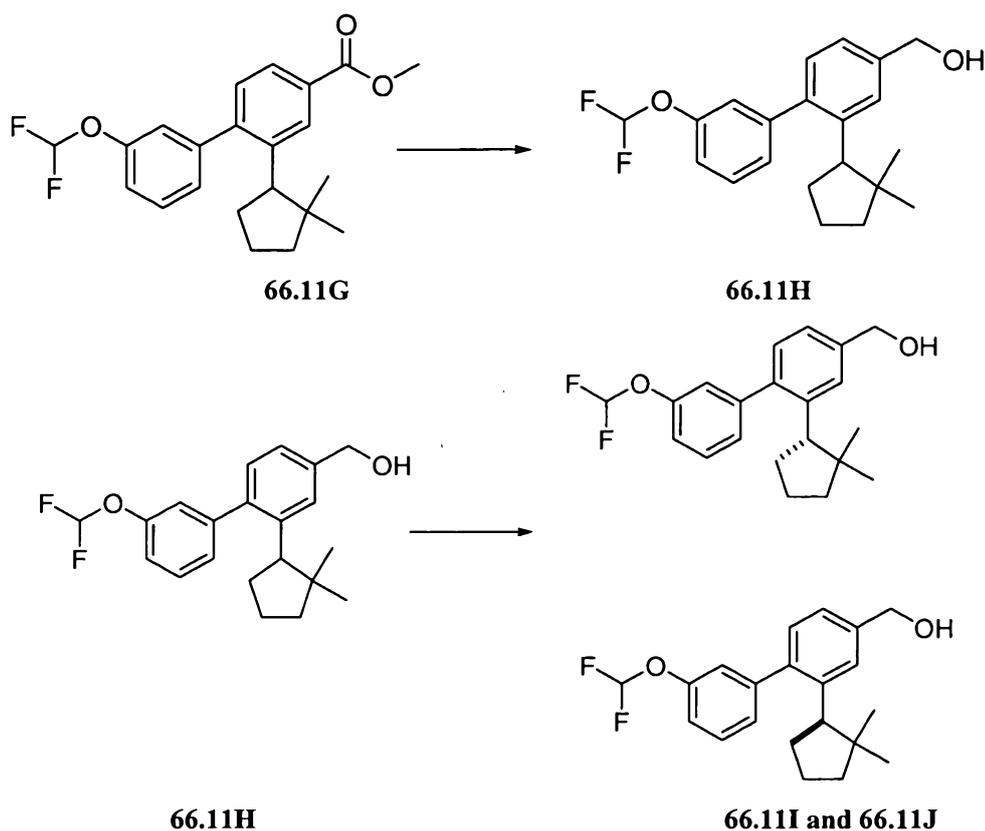


[0561] Methyl 3-(2,2-dimethylcyclopentyl)-4-(trifluoromethylsulfonyloxy)benzoate (66.11F). To a stirred solution of **66.11E** (0.93 g, 3.74 mmol) in dry DCM (10.0 mL) was added TEA (1.1 mL, 7.89 mmol) and 4-(dimethylamino)pyridine (46.2 mg, 0.378 mmol). After about 20 minutes, N-phenyl-bis(trifluoromethanesulfonimide) (1.61 g, 4.51 mmol) was added in portions. Upon complete addition, the solution was stirred at room temperature and monitored with TLC and LC-MS. After 3.5 hours, the reaction was diluted with brine and extracted three times with DCM. After drying over anhydrous magnesium sulfate and filtration, the organic solvent was removed under reduced pressure and the residue was purified with silica gel chromatography using 0-10% EtOAc in hexanes to yield **66.11F** as a colorless oil (1.21 g, 85%). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.08 (1 H, d, J=2.2 Hz), 7.95 (1 H, dd, J=8.6, 2.2 Hz), 7.35 (1 H, d, J=8.6 Hz), 3.95 (3 H, s), 3.21 (1 H, dd, J=9.8, 8.4 Hz), 2.14 (2 H, m), 1.95 (1 H, m), 1.86 (1 H, m), 1.69 (2 H, m), 1.02 (3 H, s), 0.70 (3 H, s).



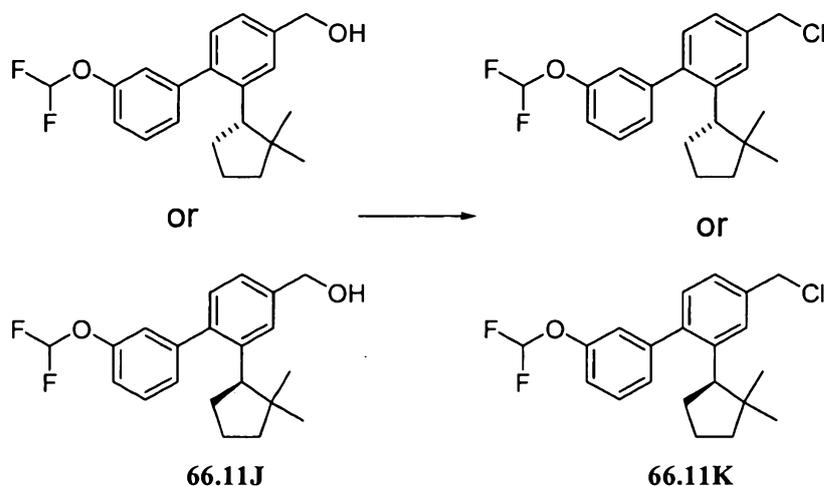
[0562] Methyl 3'-((difluoromethyl)oxy)-2-(2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-carboxylate (66.11G). A stirred mixture of **66.11F** (0.48 g, 1.26 mmol), ground S-Phos (104.8 mg, 0.255 mmol), palladium acetate (29.1 mg, 0.130 mmol), and potassium phosphate tribasic (0.6727 g, 3.17 mmol) in dry DMF (5.0 mL) was purged with argon and placed under vacuum (repeated three times). Before heating, **66.11B** (0.512 g, 1.89 mmol) was added via syringe, and then the mixture was heated to 75°C. After 16 hours, the reaction was cooled to room temperature, diluted with water and

extracted three times with EtOAc. The combined organic layers were washed twice with brine. After drying over anhydrous sodium sulfate and filtration, the organic solvent was removed under reduced pressure. The residue was purified on silica gel (0-20% EtOAc in hexanes) to yield **66.11G** as a colorless oil (308.9 mg, 65%). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ ppm 8.11 (1 H, d, $J=1.7$ Hz), 7.90 (1 H, dd, $J=7.9, 1.8$ Hz), 7.44 (1 H, m), 7.28 (1 H, m), 7.16 (2 H, m), 7.07 (1 H, s), 6.57 (1H, t, $J = 75$ Hz), 3.97 (3 H, s), 3.10 (1 H, t, $J=9.4$ Hz), 2.13 (2 H, m), 1.90 (1 H, m), 1.73 (1 H, m), 1.61 (1 H, m), 1.38 (1 H, ddd, $J=12.6, 9.4, 7.6$ Hz), 0.75 (3 H, s), 0.58 (3 H, s).

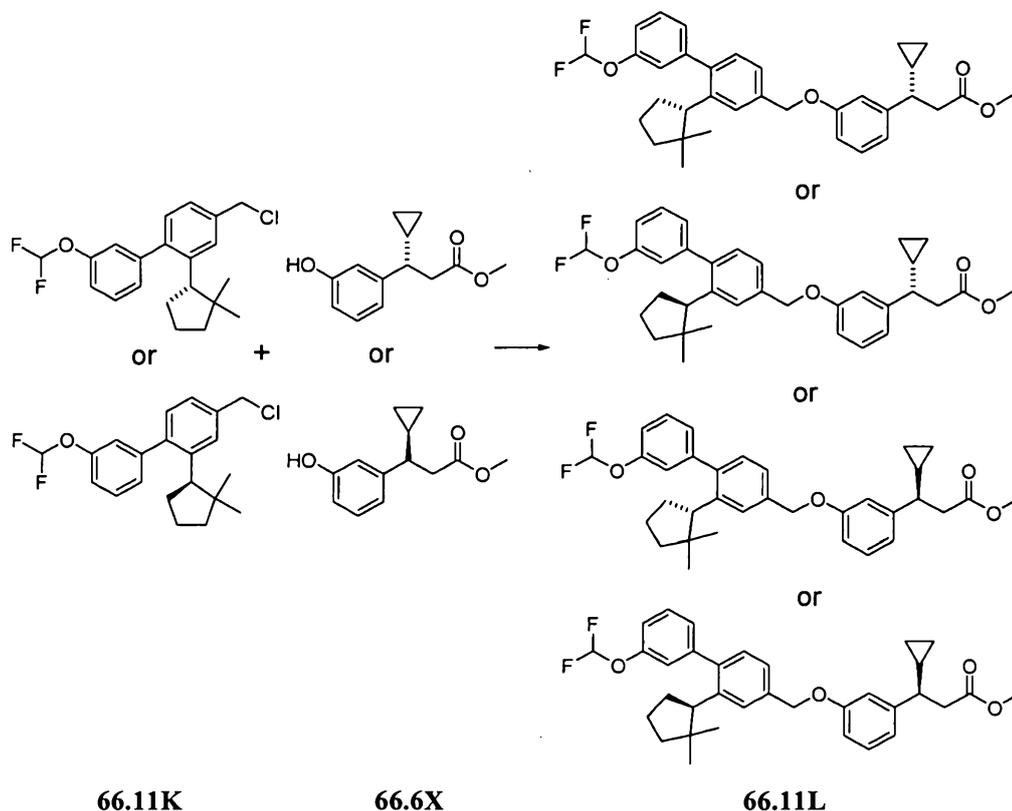


[0563] **(3'-((Difluoromethyl)oxy)-2-(2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methanol (66.11H)**. To a cooled solution of **66.11G** (308.9 mg, 0.82 mmol) in dry THF (8.0 mL) at 0°C was added LAH, 1.0 M in THF (1.70 mL, 1.70 mmol) dropwise. Upon complete addition, the reaction was maintained at 0°C and was monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction. The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified by flash chromatography

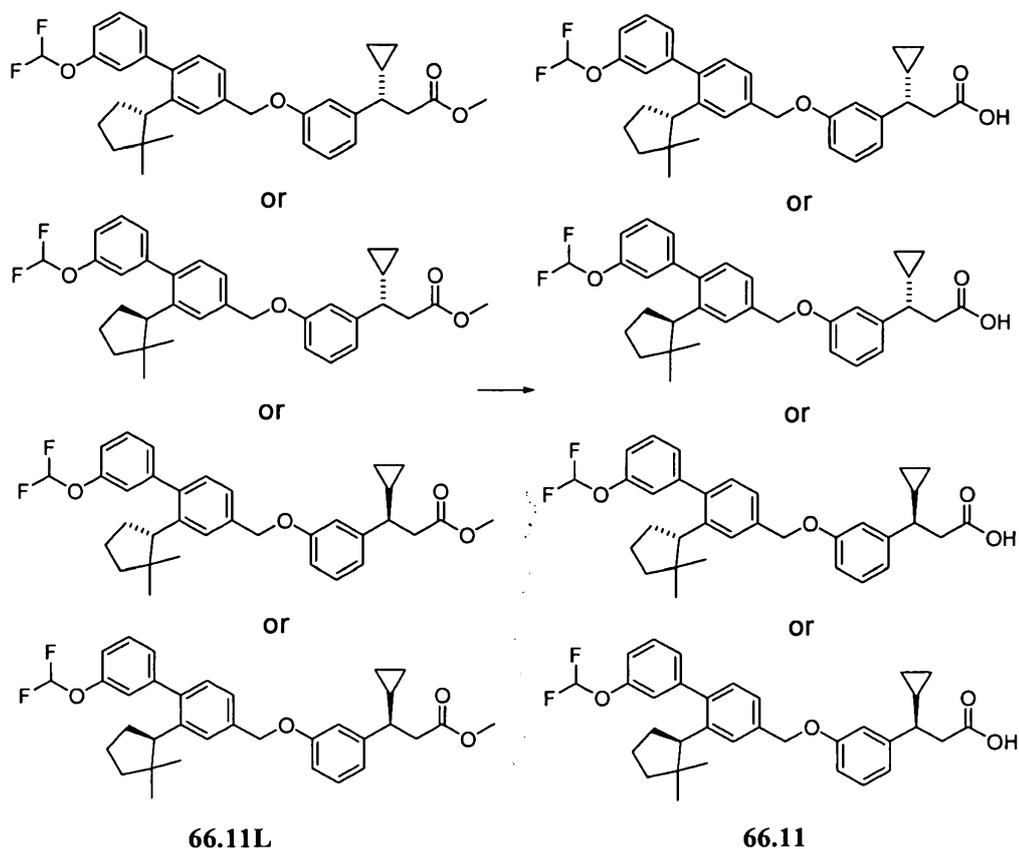
(SiO₂ gel 60, eluted with 0%-50% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to yield **66.11H** as a colorless oil (261.6 mg, 92%). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.41 (2 H, m), 7.26 (1 H, m), 7.21 (1 H, m), 7.14 (2 H, m), 7.05 (1 H, s), 6.55 (1H, t, J = 75 Hz), 4.76 (2 H, m), 3.07 (1 H, dd, J=10.3, 8.6 Hz), 2.10 (2 H, m), 1.86 (1 H, m), 1.71 (1 H, m), 1.55 (1 H, ddd, J=12.7, 8.1, 4.9 Hz), 1.37 (1 H, ddd, J=12.5, 9.5, 7.6 Hz), 0.75 (3 H, s), 0.60 (3 H, s). Chiral separation of **66.11H** was accomplished on Chiralcel-OD (3% IPA in hexane) to provide **66.11I** (peak 1) and **66.11J** (peak 2). Both enantiomers were used to synthesize example compounds, and both enantiomers gave active compounds. The enantiomer corresponding to peak 2 provided the more active example compound.



[0564] 4-(Chloromethyl)-3'-((difluoromethyl)oxy)-2-((1S)-2,2-dimethylcyclopentyl)-1,1'-biphenyl or 4-(chloromethyl)-3'-((difluoromethyl)oxy)-2-((1R)-2,2-dimethylcyclopentyl)-1,1'-biphenyl (**66.11K**). To a solution of **66.11J** (112.7 mg, 0.325 mmol) in dry DCM (4.0 mL) and dry DMF (0.03 mL) was added thionyl chloride (0.06 mL, 0.823 mmol) at 0°C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to yield **66.11K** (99.5 mg, 84 %). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.42 (2 H, m), 7.25 (1 H, d, J=2.0 Hz), 7.19 (1 H, m), 7.11 (2 H, dd, J=7.8, 2.0 Hz), 7.03 (1 H, s), 6.54 (1H, t, J= 74 Hz), 4.66 (2 H, m), 3.04 (1 H, dd, J=10.4, 8.4 Hz), 2.14 (2 H, m), 1.88 (1 H, m), 1.73 (1 H, m), 1.54 (2 H, ddd, J=12.7, 8.2, 4.9 Hz), 1.41 (1 H, m), 0.73 (3 H, s), 0.56 (3 H, s).



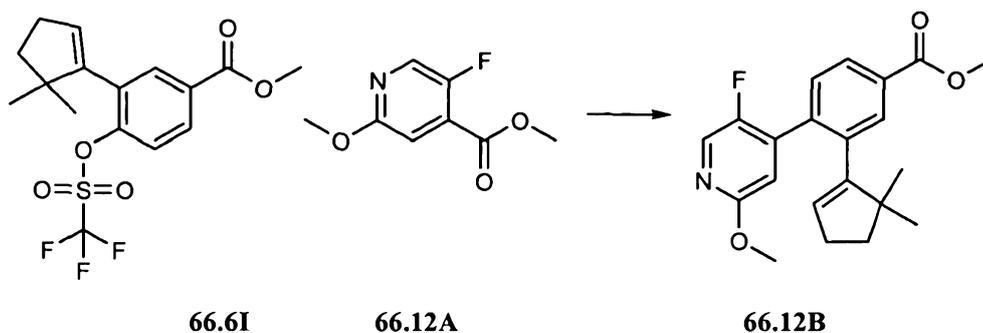
[0565] **Methyl (3S)-3-cyclopropyl-3-(3-(((3'-((difluoromethyl)oxy)-2-((1S)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3S)-3-cyclopropyl-3-(3-(((3'-((difluoromethyl)oxy)-2-((1R)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((3'-((difluoromethyl)oxy)-2-((1S)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((3'-((difluoromethyl)oxy)-2-((1R)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.11L).** To a vial containing **66.6X** (0.0156 g, 0.0708 mmol) in dry DMF (1.0 mL) was added cesium carbonate (0.0299 g, 0.0918 mmol). The mixture was stirred at room temperature for 10 minutes, then **66.11K** (0.0297 g, 0.0814 mmol) was added. After 22 hours, the reaction was diluted with water then extracted five times with EtOAc. The combined organic layers were then washed one time with brine and dried over anhydrous magnesium sulfate. The solid was filtered off, and the solvent was concentrated. The residue was purified by silica gel flash chromatography (0-50% EtOAc/hexane) to yield **66.11L** (20.5 mg, 53 %).



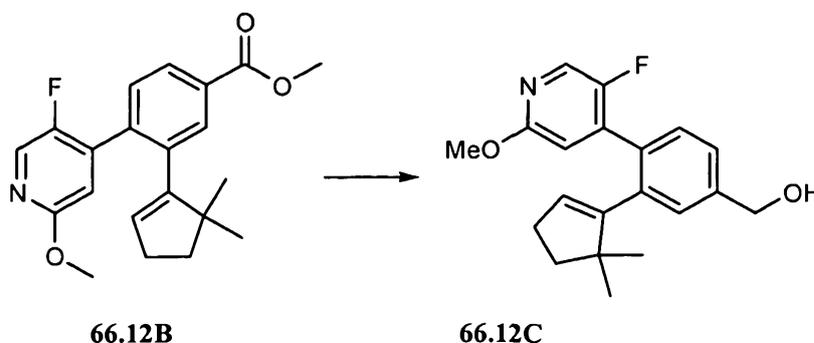
[0566] (3S)-3-Cyclopropyl-3-(3-(((3'-((difluoromethyl)oxy)-2-((1S)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((3'-((difluoromethyl)oxy)-2-((1R)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((3'-((difluoromethyl)oxy)-2-((1S)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((3'-((difluoromethyl)oxy)-2-((1R)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (**66.11**). A pre-mixed solution of 2M NaOH (0.3 mL), THF (0.5 mL), and MeOH (0.5 mL) was added to a vial containing **66.11L** (0.0205 g, 0.0374 mmol). This solution was stirred at room temperature and monitored with TLC and LC-MS. After 24 hours, the mixture was diluted with water and acidified with 1M aqueous HCl solution, then extracted five times with EtOAc. The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by silica gel flash chromatography (0-40% EtOAc/hexane) to yield **66.11** (12.8 mg, 64 %). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.45 (2 H, m), 7.32 (1 H, dd, J=7.8, 2.0

Hz), 7.28 (3 H, m), 7.15 (2 H, m), 7.04 (1 H, s), 6.93 (3 H, m), 6.54 (1H, t, J= 78 Hz), 5.10 (2 H, s), 3.05 (1 H, dd, J=10.4, 8.4 Hz), 2.86 (2 H, m), 2.44 (1 H, m), 2.13 (2 H, m), 1.87 (1 H, m), 1.73 (1 H, m), 1.52 (1 H, ddd, J=12.7, 8.2, 4.9 Hz), 1.40 (1 H, m), 1.09 (1 H, m), 0.69 (3 H, s), 0.65 (4 H, m), 0.49 (1 H, m), 0.30 (1 H, dq, J=9.7, 4.8 Hz), 0.16 (1 H, dq, J=9.9, 4.8 Hz). MS ESI (neg.) m/e: 532.9 (M-H)⁺.

[0567] **Example 66.12**

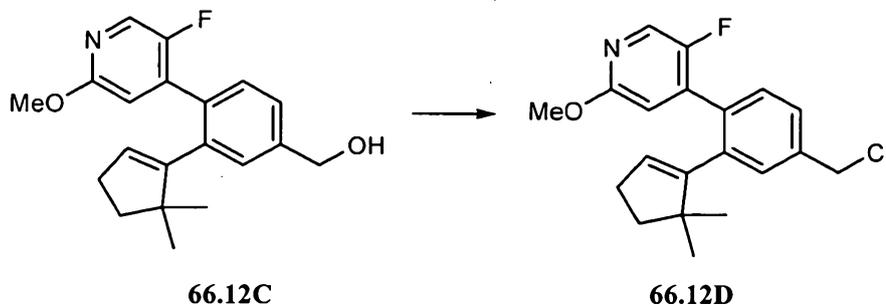


[0568] **Methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxy-4-pyridyl)benzoate (66.12B)**. To a flask with methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-(trifluoromethylsulfonyloxy)benzoate **66.6I** (404 mg, 1068 μmol) was added Pd(PPh₃)₄ (123 mg, 107 μmol), potassium carbonate (443 mg, 3203 μmol), 5-fluoro-2-methoxy-4-pyridylboronic acid **66.12A** (456 mg, 2669 μmol , commercially available from Asymchem). The mixture was then degassed, and DMF (3 mL) was added. The reaction was stirred overnight at 87°C and worked up with EtOAc and water. Silica gel chromatography (0-50% EtOAc/Hexanes) afforded methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxy-4-pyridyl)benzoate **66.12B** 295 mg (78%).

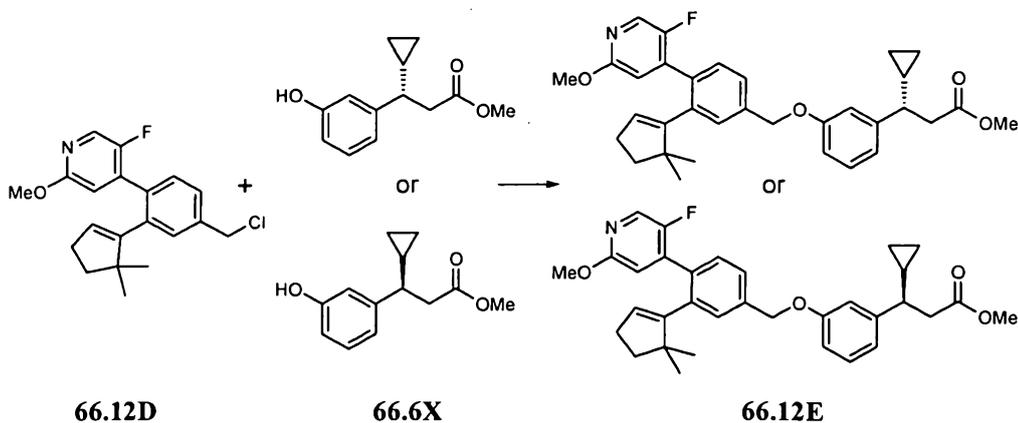


[0569] **(3-(5,5-Dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxy-4-pyridyl)phenyl)methanol (66.12C)**. To methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxy-4-pyridyl)benzoate **66.12B** (295 mg, 830 μmol) was added THF. The

mixture was cooled to 0°C, and LAH (1660 μ L, 1660 μ mol) was added dropwise. The reaction was stirred at room temperature for 1 hour, and was quenched with water and a small amount of Rochelle's salt solution. Purification with silica gel chromatography afforded (3-(5,5-dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxypyridin-4-yl)phenyl)methanol **66.12C** (201 mg) as an oil (74%).

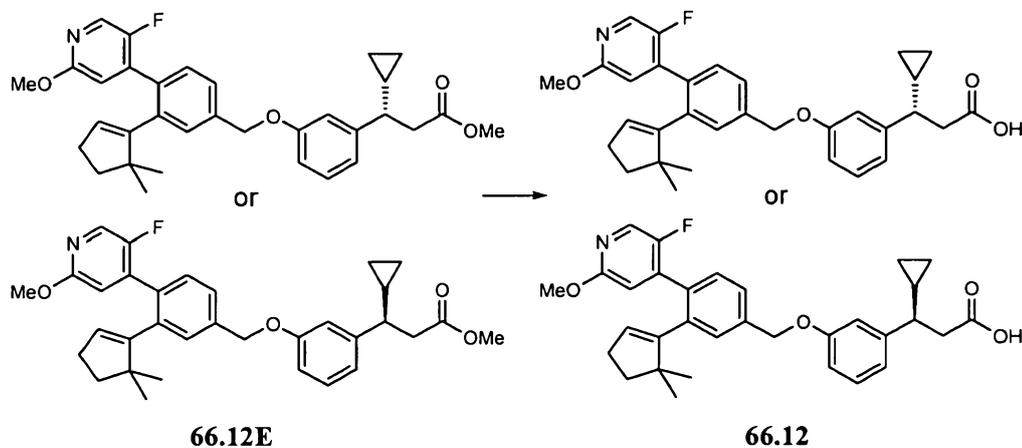


[0570] **4-(4-(Chloromethyl)-2-(5,5-dimethylcyclopent-1-enyl)phenyl)-5-fluoro-2-methoxypyridine (66.12D)**. To (3-(5,5-dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxypyridin-4-yl)phenyl)methanol **66.12C** (34.5 mg, 105 μ mol) was added DCM (1.1 mL) and DMF (8.2 μ L, 105 μ mol) followed by thionyl chloride (15 μ L, 211 μ mol) in an ice bath. The reaction was then stirred at room temperature for 1 hour. The reaction was concentrated and directly purified on silica gel to afford 4-(4-(chloromethyl)-2-(5,5-dimethylcyclopent-1-enyl)phenyl)-5-fluoro-2-methoxypyridine **66.12D** (36 mg) as an oil (99%).



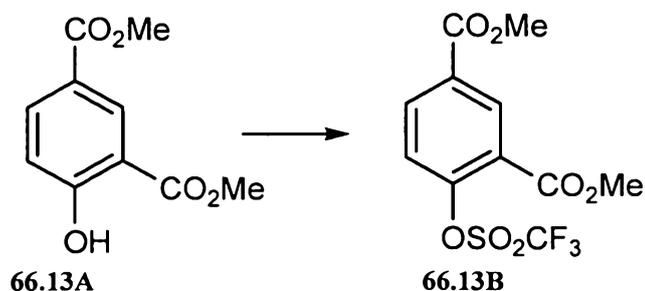
[0571] **(3S)-Methyl 3-(3-(3-(5,5-dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxypyridin-4-yl)benzyloxy)phenyl)-3-cyclopropylpropanoate or (3R)-methyl 3-(3-(3-(5,5-dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxypyridin-4-yl)benzyloxy)phenyl)-3-cyclopropylpropanoate (66.12E)**. To a flask with 4-(4-(chloromethyl)-2-(5,5-dimethylcyclopent-1-enyl)phenyl)-5-fluoro-2-methoxypyridine

66.12D (36 mg, 104 μ mol) and cesium carbonate (41 mg, 125 μ mol) was added a DMF solution of **66.6X** (23 mg, 104 μ mol). The reaction was stirred overnight at room temperature. Water was added followed by extraction with EtOAc. The product was purified by silica gel chromatography to afford **66.12E** 53 mg an oil (96%).



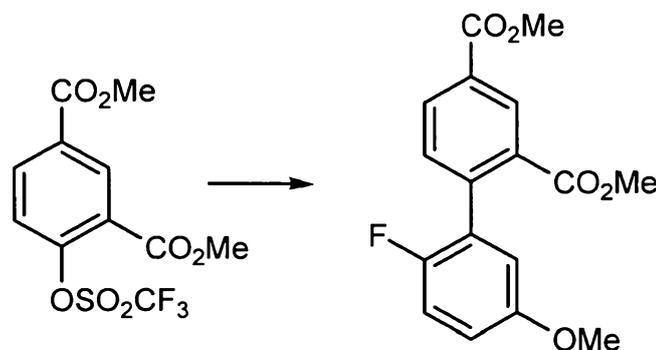
[0572] **(3S)-3-(3-(3-(5,5-Dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxyphenyl)benzyloxy)phenyl)-3-cyclopropylpropanoic acid** or **(3R)-3-(3-(3-(5,5-dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxyphenyl)benzyloxy)phenyl)-3-cyclopropylpropanoic acid** (**66.12**). To a flask with **66.12E** was added 1 mL THF, 0.5 mL MeOH and 0.5 mL 1N LiOH. The mixture was stirred overnight. 1N HCl was added to adjust the pH to about 4. The reaction was then extracted with EtOAc. The product was purified by silica gel chromatography to afford **66.12** (46 mg) as a white solid (89%). MS ESI (neg.) m/e: 514.2 (M-H)⁺.

[0573] **Example 66.13**

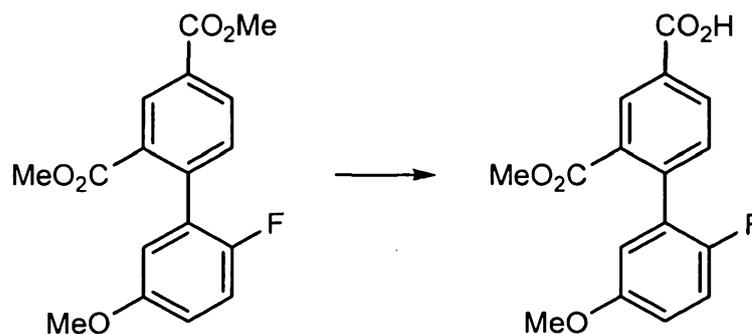


[0574] **Dimethyl 4-(trifluoromethylsulfonyloxy)isophthalate** (**66.13B**). To a stirred solution of dimethyl 4-hydroxyisophthalate **66.13A** (commercially available from Chem Service) (37.7 g, 179 mmol) in DCM (256 mL, 179 mmol) at 23°C was added TEA (30 mL, 215 mmol), and a catalytic amount of DMAP. N-phenyltriflimide (70 g, 197

mmol) was then added, and stirring was continued at room temperature for 21 hours. The solvent was removed, and the residue was purified on silica gel (0-10% EtOAc in hexanes) to yield **66.13B** dimethyl 4-(trifluoromethylsulfonyloxy)isophthalate as a colorless oil (59.00 g, 96% yield). MS ESI (pos.) m/e: 360.0 (M+H₂O)⁺, 343.0 (M+H)⁺.

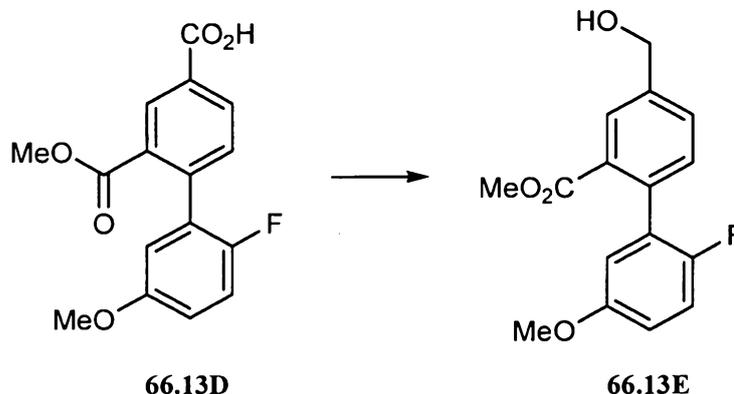
**66.13B****66.13C**

[0575] **Dimethyl 2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2,4-dicarboxylate (66.13C)**. To a stirred solution of dimethyl 4-(trifluoromethylsulfonyloxy)isophthalate **66.13B** (39.00 g, 114 mmol) in DMF (228 mL, 114 mmol) at 23°C was added 2-fluoro-5-methoxyphenylboronic acid (29 g, 171 mmol)(commercially available from Aldrich), potassium carbonate (47 g, 342 mmol), followed by tetrakis(triphenylphosphine)palladium (9.2 g, 8.0 mmol). The mixture was heated to 90°C and stirring was continued for 18 hours. The reaction was cooled to room temperature. Water was added to the reaction, and the resulting mixture was extracted with EtOAc. The organic layer was dried over MgSO₄ and concentrated. The crude product was purified by silica gel flash chromatography (0-20% EtOAc/hexane) to afford dimethyl 2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2,4-dicarboxylate **66.13C** as a clear oil (32.00 g, 88% yield). MS ESI (pos.) m/e: 319.1 (M+H)⁺.

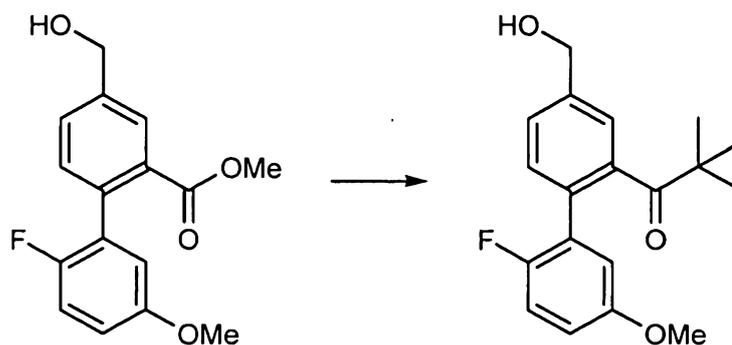


66.13C**66.13D**

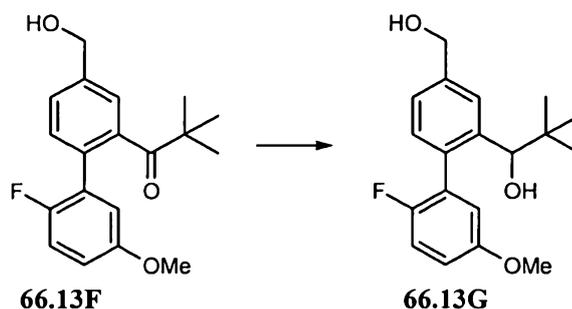
[0576] **2'-Fluoro-5'-(methoxy)-2-((methoxy)carbonyl)-1,1'-biphenyl-4-carboxylic acid (66.13D)**. To a stirred solution of **66.13C** (36.50 g, 115 mmol) in THF (70.0 mL, 854 mmol) and MeOH (70.0 mL, 1730 mmol) at 0°C was added potassium hydroxide (63 mL, 126 mmol) slowly to maintain the temperature below 6°C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 15 hours. The reaction mixture was concentrated in vacuo. 1N HCl was added to the aqueous phase and the resulting mixture was extracted with EtOAc. The organic layer was dried over MgSO₄, and concentrated in vacuo to give 2'-fluoro-5'-(methoxy)-2-((methoxy)carbonyl)-1,1'-biphenyl-4-carboxylic acid **66.13D** as a white solid (35.00 g, 100% yield). MS ESI (pos.) m/e: 322.1 (M+H₂O)⁺, 305.0 (M+H)⁺.

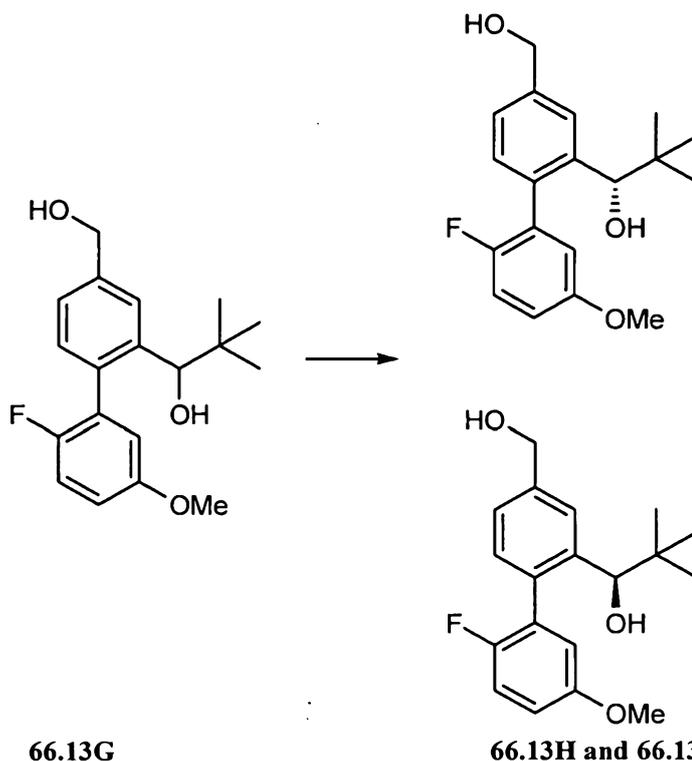


[0577] **Methyl 2'-fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-carboxylate (66.13E)**. To a stirred solution of 2'-fluoro-5'-(methoxy)-2-((methoxy)carbonyl)-1,1'-biphenyl-4-carboxylic acid **66.13D** (35.60 g, 117 mmol) in THF (1170 mL, 117 mmol) at 0°C was added borane-THF (234 mL, 234 mmol). The reaction was warmed to 23°C and stirring was continued for 6 hours. The mixture was then concentrated in vacuo. 1 N HCl was added to the reaction, and the mixture was extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified on silica gel (0-40% EtOAc in hexane) to give methyl 2'-fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-carboxylate **66.13E** as a clear oil (30.00 g, 88% yield). MS ESI (pos.) m/e: 308.0 (M+H₂O)⁺, 291.1 (M+H)⁺.

**66.13E****66.13F**

[0578] **1-(2'-Fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanone (66.13F)**. To a stirred solution of methyl 2'-fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-carboxylate **66.13E** (2.00 g, 7 mmol) in THF (138 mL, 7 mmol) at -78°C was added t-butyllithium (1.7 M in pentane, 9 mL, 14 mmol). Stirring was continued for 3 hours. A saturated solution of ammonium chloride was added to quench the reaction, and the resulting mixture was extracted with EtOAc. The combined organic layers were dried over MgSO_4 , filtered, and concentrated in vacuo to give the crude product. The crude product was purified by silica gel flash chromatography (0-20% EtOAc/hexane) to afford 1-(2'-Fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanone **66.13F** as a clear oil (2.00 g, 92% yield). MS ESI (pos.) m/e: 334.1 ($\text{M}+\text{H}_2\text{O}$)⁺, 317.2 ($\text{M}+\text{H}$)⁺.

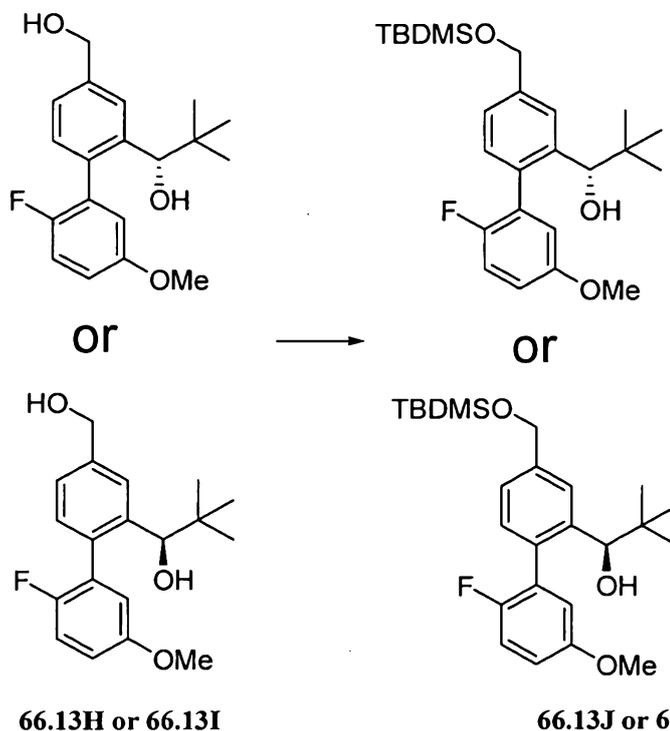
**66.13F****66.13G**



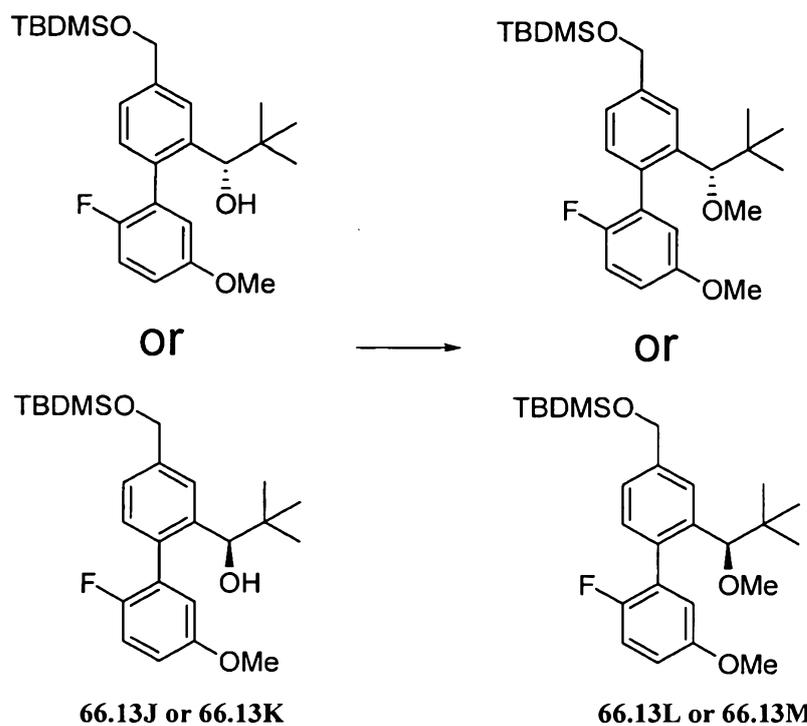
66.13G **66.13H and 66.13I**

[0579] **1-(2'-Fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol (66.13G), and (1R)-1-(2'-fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol and (1S)-1-(2'-fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol (66.13H and 66.13I).** To a stirred solution of 1-(2'-fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanone **66.13F** (2.00 g, 6.3 mmol) in THF (63 mL, 6.3 mmol) at 0°C was added LAH (1.0 M in THF, 13 mL, 13 mmol). Stirring was continued for 2 hours. 1N NaOH (aq) was added to the mixture, and the resulting mixture was extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo to give the crude product. The crude product was purified by silica gel flash chromatography (0-30% EtOAc/hexane) to afford 1-(2'-fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol **66.13G** (1.50 g, 75% yield) as a white solid. MS ESI (pos.) m/e: 336.2 (M+H₂O)⁺. Chiral separation of **66.13G** was accomplished on Chiracel-OD (4%IPA in hexane) to provide **66.13H** and **66.13I**. Both enantiomers were used to synthesize example compounds, and both enantiomers gave active example compounds. However, the enantiomer corresponding to peak 2 provided the most active example compounds.

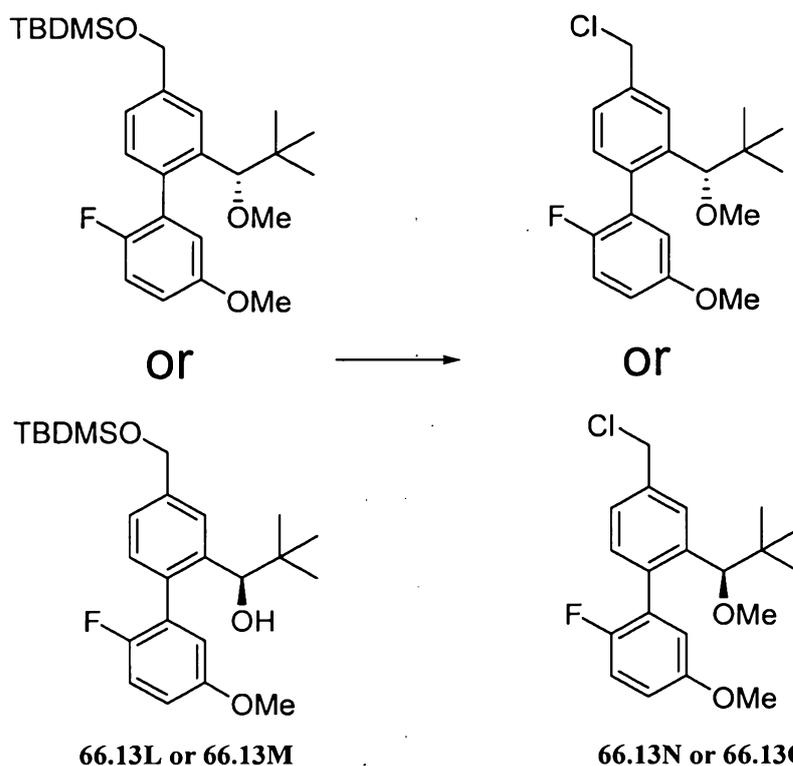
Analytical column (Chiracel-OD (4%IPA in hexane, 45 min run) Peak 1-18.5 mins, Peak 2-24.5 mins).¹



[0580] (1S)-1-(4-(((1,1-Dimethylethyl)(dimethyl)silyl)oxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol or (1R)-1-(4-(((1,1-dimethylethyl)(dimethyl)silyl)oxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol (66.13J or 66.13K). To a stirred solution of (1R)-1-(2'-fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol or (1S)-1-(2'-fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol (66.13H or 66.13I) (0.300 g, 0.9 mmol) in DCM (10.00 mL, 155 mmol) at 23°C was added tert-butyldimethylsilyl chloride (0.2 mL, 1 mmol), followed by TEA (0.2 mL, 1 mmol) and DMAP (0.01 g, 0.09 mmol). Stirring was continued for 16 hours. The mixture was then concentrated in vacuo to give the crude product. The crude product was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to afford (1S)-1-(4-(((1,1-dimethylethyl)(dimethyl)silyl)oxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol or (1R)-1-(4-(((1,1-dimethylethyl)(dimethyl)silyl)oxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol **66.13J** or **66.13K** (0.375 g, 92% yield). MS ESI (pos.) m/e: 450.2 (M+H₂O)⁺.

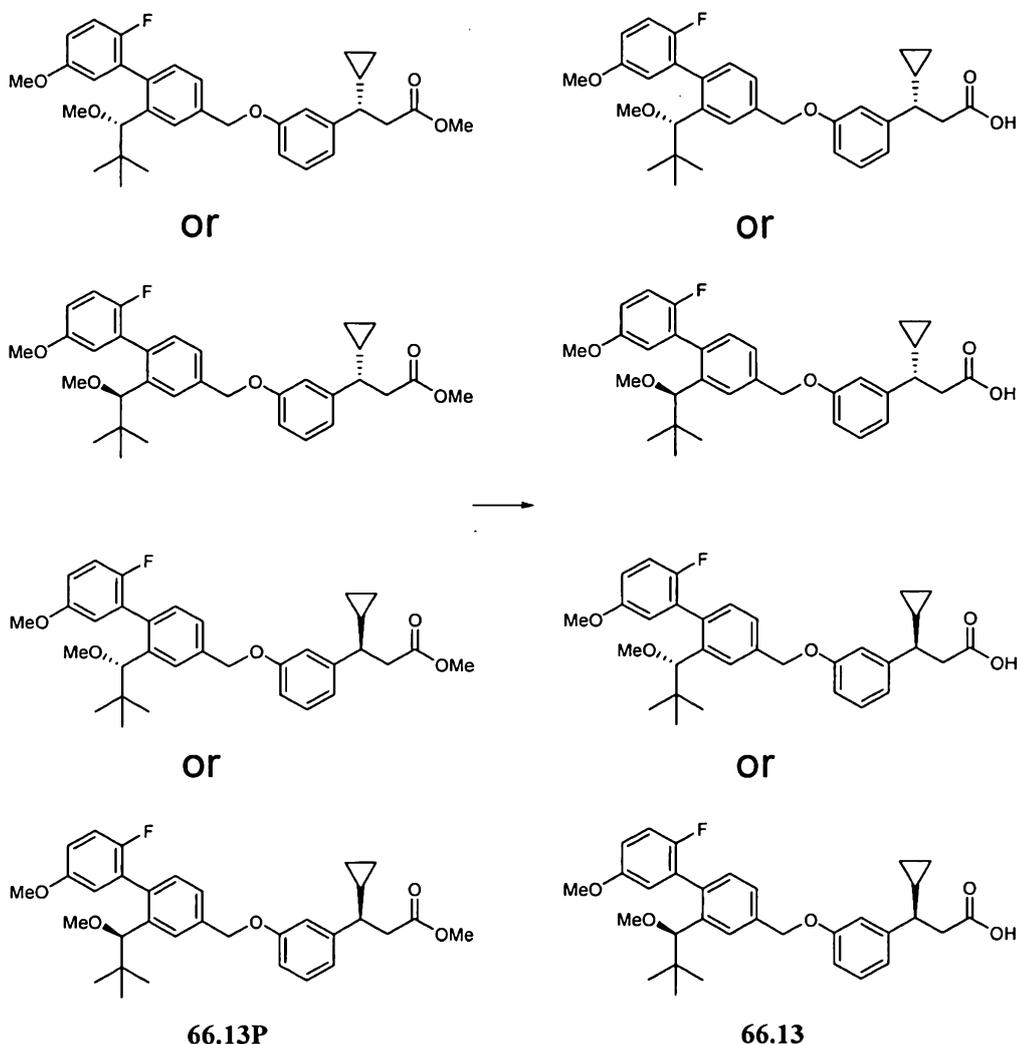


[0581] (1,1-Dimethylethyl)((2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxydimethylsilane or (1,1-dimethylethyl)((2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxydimethylsilane (**66.13L** or **66.13M**). To a stirred solution of **66.13J** or **66.13K** (0.110 g, 0.25 mmol) in DMF (2.00 mL, 26 mmol) at 23°C was added iodomethane (0.069 g, 0.50 mmol), followed by sodium hydride (0.012 g, 0.50 mmol). Stirring was continued at 50°C for 21 hours. Water was added to the mixture, and the resulting mixture was extracted with EtOAc. The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo to give the crude product. The crude product was purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **66.13L** or **66.13M** (0.051 g, 45% yield).



[0582] 4-(Chloromethyl)-2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (66.13N or 66.13O). To a stirred solution of 66.13L or 66.13M (0.082 g, 0.18 mmol) in DCM (2.00 mL, 31 mmol) at 23°C was added DMF (0.0014 mL, 0.018 mmol) followed by thionyl chloride (0.027 mL, 0.37 mmol). Stirring was continued for one hour. The reaction mixture was then concentrated in vacuo. The residue was purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford 66.13N or 66.13O (0.063 g, 98% yield).

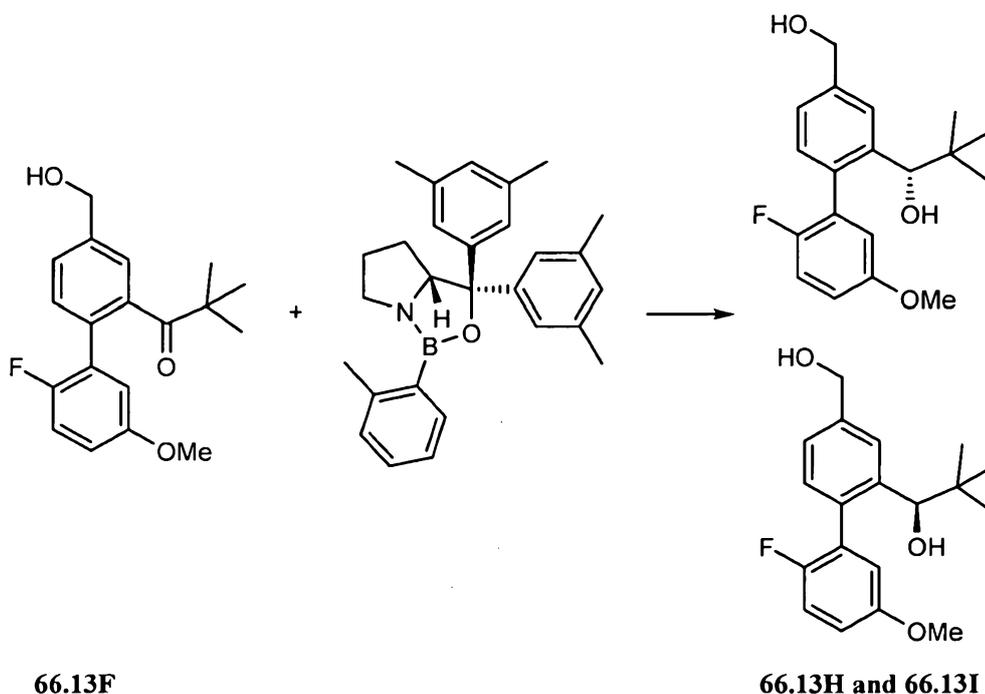
extracted with EtOAc. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified on silica gel (0%-20% EtOAc/hexane) to give **66.13P** (0.048 g, 100% yield). MS ESI (pos.) m/e: 557.3 (M+Na)⁺.



[0584] (3S)-3-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-

dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.13). To a stirred solution of **66.13P** (0.049 g, 0.092 mmol) in THF (2.00 mL, 24 mmol) and EtOH (2.00 mL, 0.092 mmol) at 23°C was added LiOH (0.092 mL, 0.092 mmol). Stirring was continued at 23 °C for 16 hours. The reaction mixture was then concentrated in vacuo. 1N HCl was added to the mixture, and the resulting mixture was extracted with EtOAc. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified on silica gel (0%-20% EtOAc/hexane) to **66.13** (0.0343 g, 72% yield). MS ESI (neg.) m/e: 519.2 (M-H)⁺.

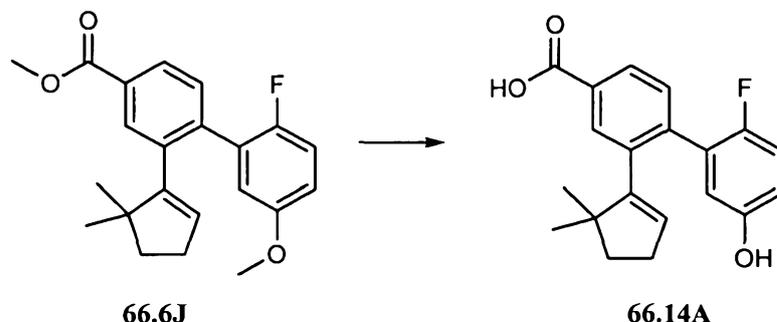
[0585] Asymmetric Synthesis of 66.13H or 66.13I



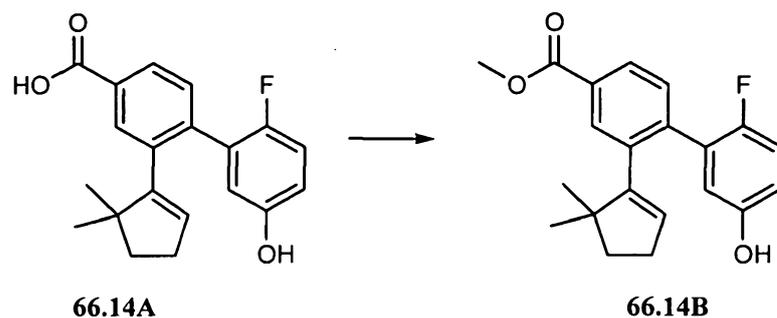
[0586] (1R)-1-(2'-Fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol and (1S)-1-(2'-fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol (66.13H and 66.13I). To a stirred solution of **66.13F** (0.050 g, 0.2 mmol) in THF (2 ml, 0.2 mmol) at 0°C was added (R)-3,3-bis(3,5-dimethylphenyl)-1-o-tolyl-hexahydropyrrolo[1,2-c][1,3,2]oxazaborole in toluene (0.02 ml, 0.02 mmol, 1.0M, commercially available from Aldrich), followed by dropwise addition of borane in THF (0.2 ml, 0.2 mmol). The reaction was then stirred at 23°C for 4 hours. The reaction was then quenched with 1N HCl (aq). The reaction mixture was extracted with EtOAc, dried over MgSO₄, filtered, and concentrated in

vacuo. The residue was purified on silica gel (0%-20% EtOAc/hexane) to yield **66.13H** or **66.13I** (0.045 g, 89% yield). Chiral HPLC determined that the major product was the desired more potent enantiomer with an enantiomeric excess of 85%.

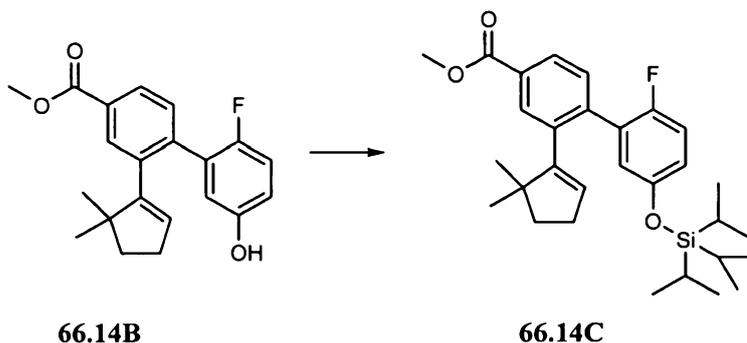
[0587] **Example 66.14**



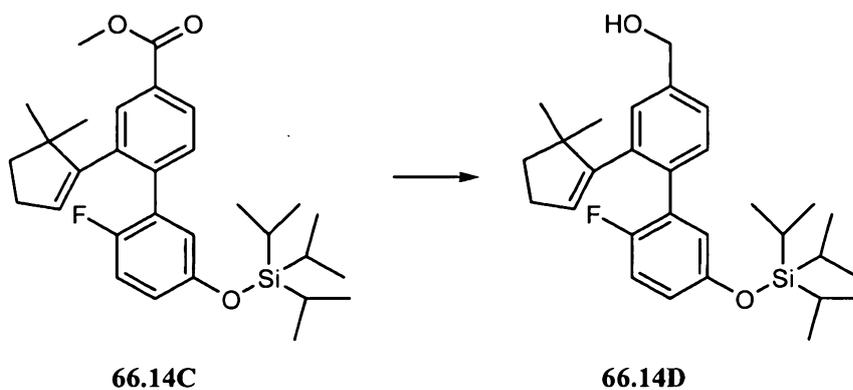
[0588] **2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-hydroxy-1,1'-biphenyl-4-carboxylic acid (66.14A)**. To a stirred solution of **66.6J** (300.0 mg, 846 μmol) in DCM (10 mL) at 0°C was added boron tribromide (3809 μL , 3809 μmol). The reaction was stirred for two hours and then pH 7 buffer was added to the mixture at 0°C, and the mixture was extracted with DCM. The combined organic layers were dried over MgSO_4 , concentrated in vacuo, and the residue was purified on silica gel (0%-20% EtOAc/hexane) to give **66.14A**.



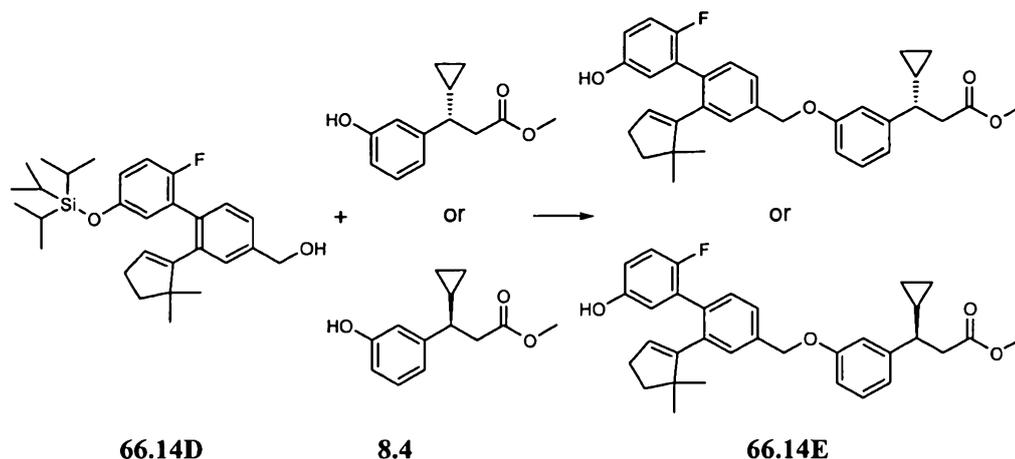
[0589] **Methyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-hydroxy-1,1'-biphenyl-4-carboxylate (66.14B)**. To a flask containing **66.14A** (75 mg, 230 μmol) in MeOH (2 mL) was added sulfuric acid (0.61 μL , 11 μmol), and the mixture was stirred at reflux overnight. The reaction was concentrated and then purified by silica gel chromatography (0 to 30% EtOAc/ Hexanes) to provide **66.14B** (77.0 mg, 98% yield).



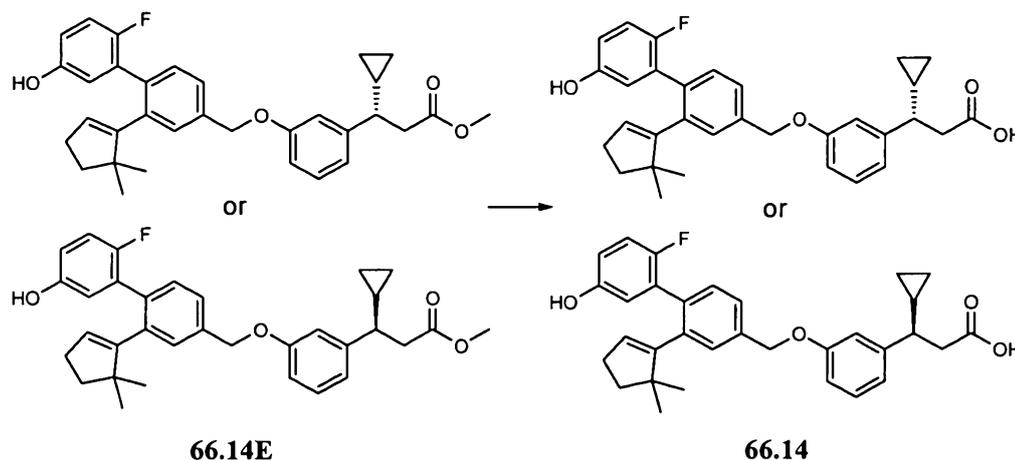
[0590] **Methyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-((tris(1-methylethyl)silyl)oxy)-1,1'-biphenyl-4-carboxylate (66.14C).** To **66.14B** (77.0 mg, 226 μmol) in DMF (10 mL) was added imidazole (30.8 mg, 452 μmol) and then triisopropylsilyl chloride (58.1 μL , 271 μmol). The resulting mixture was then stirred for 4 hours. The reaction was diluted with EtOAc and washed with 1N HCl, water, and brine. The organic phase was dried over sodium sulfate, filtered, concentrated, and purified by silica gel chromatography (0 to 10% EtOAc/ Hexanes) to provide **66.14C** (90.0 mg, 80.1% yield).



[0591] **(2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-((tris(1,1-dimethylethyl)silyl)oxy)-1,1'-biphenyl-4-yl)methanol (66.14D).** To **66.14C** (90.0 mg, 167 μmol) in THF (1 mL) at 0°C was added LAH (1.0M solution in THF)(251 μL , 251 μmol). The reaction was stirred for one hour and then carefully diluted with water, extracted with EtOAc, washed with brine, dried over sodium sulfate, filtered, and concentrated to provide **66.14D** (64.0 mg, 75.0% yield).



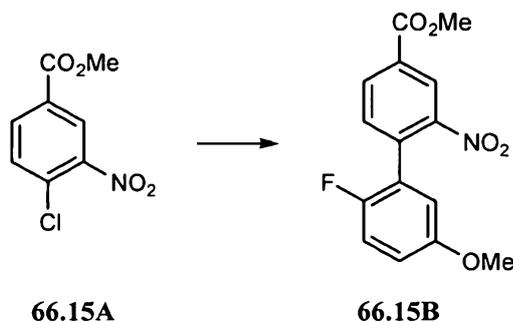
[0592] **Methyl (3S)-3-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-hydroxy-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-hydroxy-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.14E).** To a flask containing **8.4** (30.1 mg, 137 μ mol), **66.14D** (64.0 mg, 137 μ mol), and triphenylphosphine (polymer supported)(68.3 mg, 205 μ mol) in DCM (1 mL) was added diethyl azodicarboxylate (32.3 μ L, 205 μ mol) at 0°C. The reaction was then allowed to warm to room temperature and stirred for 1 hour. The reaction was concentrated and then purified by silica gel chromatography (0 to 20% EtOAc/ Hexanes) to provide **66.14E** (66.3 mg, 94.4% yield).



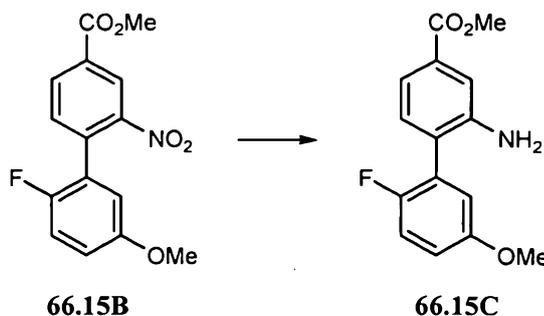
[0593] **(3S)-3-Cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-hydroxy-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-hydroxy-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.14).** To a solution of **66.14E** (5.1 mg, 9.9 μ mol) in THF/MeOH (2/1) (1.5 mL) was added LiOH (0.500 mL, 500 μ mol).

The resulting mixture was stirred overnight at 23 °C, quenched with excess 1N HCl, and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography (0 to 40% EtOAc/hexanes) to afford a **66.14** (4.5 mg, 91% yield). MS ESI (neg.) m/e: 499.1 (M-H).

[0594] **Example 66.15**

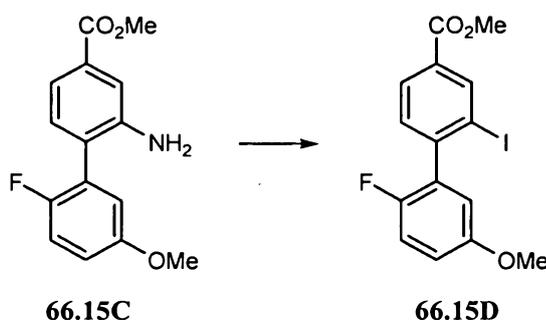


[0595] **Methyl 2'-fluoro-5'-(methoxy)-2-nitro-1,1'-biphenyl-4-carboxylate (66.15B)**. To a stirred solution of methyl 4-chloro-3-nitrobenzoate (10.00 g, 46 mmol)(commercially available from Aldrich) in DMF (15.00 mL, 194 mmol) at 23°C was added 2-fluoro-5-methoxyphenylboronic acid (12 g, 70 mmol)(commercially available from Aldrich), and potassium carbonate (19 g, 139 mmol). Tetrakis(triphenylphosphine)palladium (2.1 g, 1.9 mmol) was then added to the mixture, and the mixture was heated at 90°C for 18 hours. The mixture was then cooled to room temperature, diluted with brine and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was purified on silica gel (0-40% EtOAc in hexanes) to yield **66.15B** as a colorless oil (14.00 g, 99% yield).

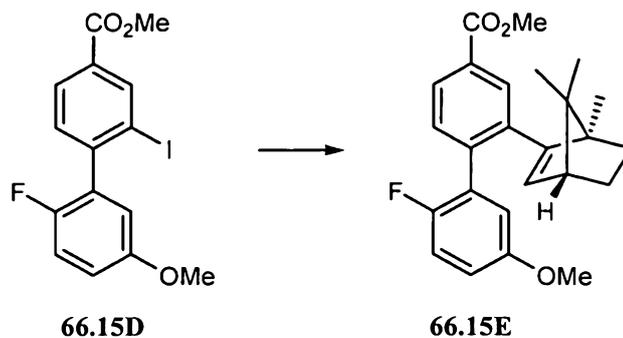


[0596] **Methyl 2-amino-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.15C)**. To a stirred solution of **66.15B** (1.00 g, 3.3 mmol) in acetic acid (2.00 mL, 35

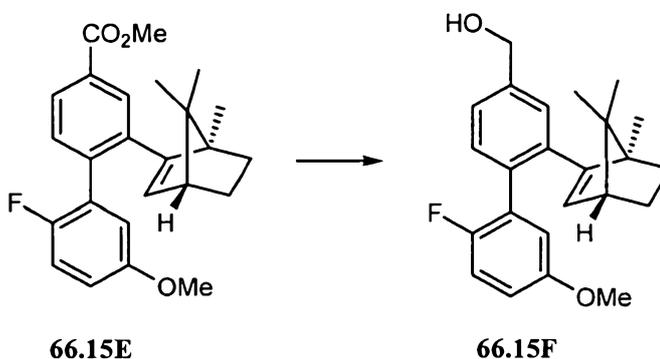
mmol) at 23°C was added DME (15.00 mL, 144 mmol), EtOH (10.00 mL), followed by tin(II) chloride (4.7 g, 25 mmol). The mixture was heated at 60°C for 17 hours. After which, the reaction was cooled to room temperature. The reaction was diluted with water and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure to give the product **66.15C** (0.90 g, 100% yield).



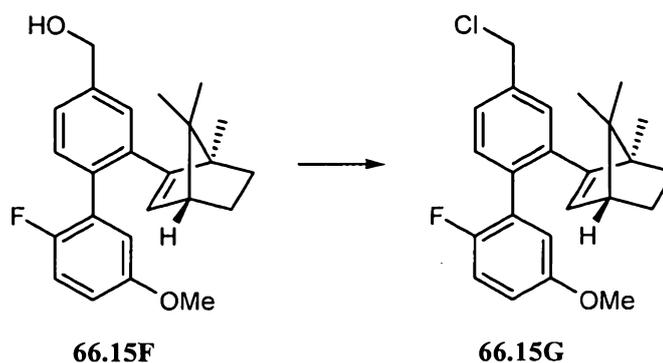
[0597] **Methyl 2'-fluoro-2-iodo-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.15D)**. To a stirred solution of **66.15C** (1.00 g, 3.6 mmol) in DME (10.00 mL, 96 mmol) at 23°C was added sulfuric acid (0.19 mL, 3.6 mmol) in water (8 mL), followed by dropwise addition of a solution of sodium nitrite (0.38 g, 5.4 mmol) in water (2 mL) at 0°C over 30 minutes. The reaction was then stirred for 20 minutes. To the mixture was added a solution of sodium iodide (3.0 g, 20 mmol) in water (7 mL) at 0°C. The resulting mixture was then stirred for 1 hour. The reaction was quenched with sodium thiosulfate and extracted three times with diethyl ether. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was purified on silica gel (0-40% EtOAc in hexanes) to yield a colorless solid **66.15D** (0.820 g, 58% yield).



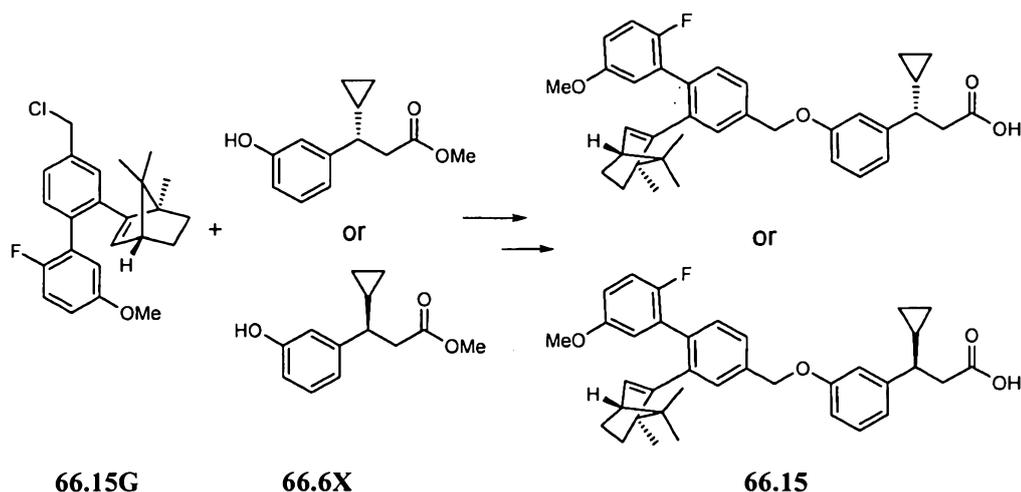
[0598] Methyl 2'-fluoro-5'-(methoxy)-2-((1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl)-1,1'-biphenyl-4-carboxylate (66.15E). To a stirred solution of **66.15D** (0.200 g, 0.52 mmol) in DMF (4.00 mL, 52 mmol) at 23°C was added (1S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-ylboronic acid (0.19 g, 1.0 mmol, commercially available from Combi-Blocks, Cat. No. BB-2567), potassium carbonate (0.21 g, 1.6 mmol), and then tetrakis(triphenylphosphine)palladium (0.060 g, 0.052 mmol). The mixture was heated at 90°C for 19 hours and then cooled to room temperature. The reaction was diluted with brine and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was purified on silica gel (0-10% EtOAc in hexanes) to yield **66.15E** as a colorless oil (0.165 g, 81% yield).



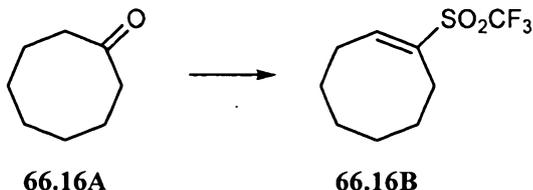
[0599] (2'-Fluoro-5'-(methoxy)-2-((1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl)-1,1'-biphenyl-4-yl)methanol (66.15F). To a stirred solution of **66.15E** (0.050 g, 0.1 mmol) in THF (4 mL) at 0°C was added LAH in THF (0.3 mL, 0.3 mmol, 1.0M). The resulting mixture was stirred for 2 hours. 1N NaOH(aq) was added to the mixture to quench it. The reaction was then extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was purified on silica gel (0-20% EtOAc in hexanes) to yield **66.15F** as a colorless oil (0.035 g, 75% yield).



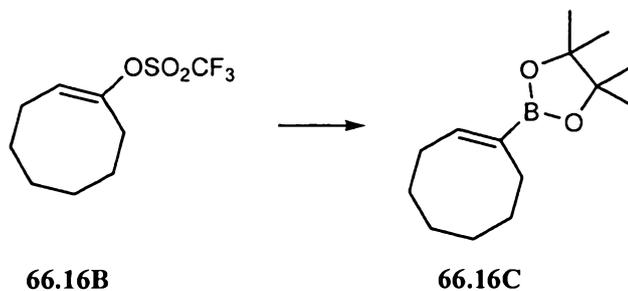
[0600] **4'-(Chloromethyl)-6-fluoro-2'-((1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl)-1,1'-biphenyl-3-yl methyl ether (66.15G).** To a stirred solution of **66.15F** (0.035 g, 0.10 mmol) in DCM (2.00 mL) and DMF (0.01 mL) at 0°C was added thionyl chloride (0.01 g, 0.10 mmol). The reaction was then stirred at room temperature for 2 hours and was then concentrated in vacuo. The resulting product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.15G** as a colorless oil (0.035 g, 95% yield).



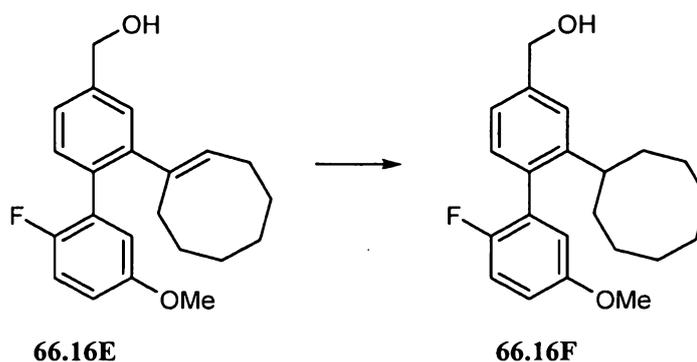
[0601] **(3S)-3-Cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-((1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-((1R,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.15).** The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (described herein) to yield **66.15** (0.0303 g, 61% yield over two steps). MS ESI (neg.) m/e: 515.2 (M-H)⁺.

[0602] Example 66.16

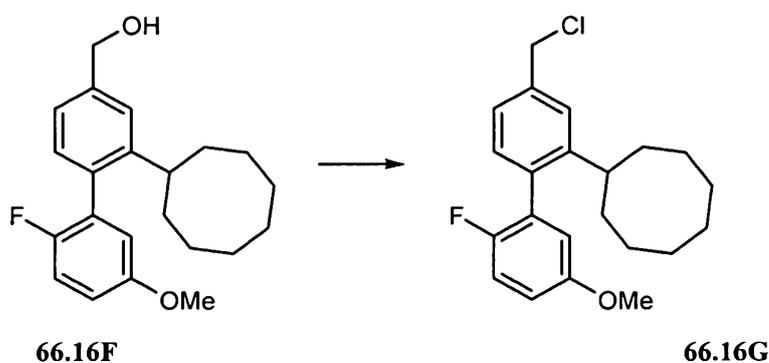
[0603] 1-Cycloocten-1-yl trifluoromethyl sulfone (66.15B). To a stirred solution of cyclooctanone (5.00 g, 40 mmol)(commercially available from Aldrich) in THF (35 mL) at -78°C was added LDA (22 mL, 44 mmol, 2.0M). The resulting solution was stirred at -78°C for 20 minutes. Then, a solution of N-phenyl-bis(trifluoromethane sulfonimide) (16 g, 44 mmol) in THF (15 mL) was added slowly at -78°C. The reaction mixture was allowed to warm to 23°C over 3 hours and then was concentrated in vacuo. The residue was diluted with water and extracted three times with hexanes. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-5% EtOAc in hexanes) to yield **66.16B** as a colorless oil (10.00 g, 98% yield).



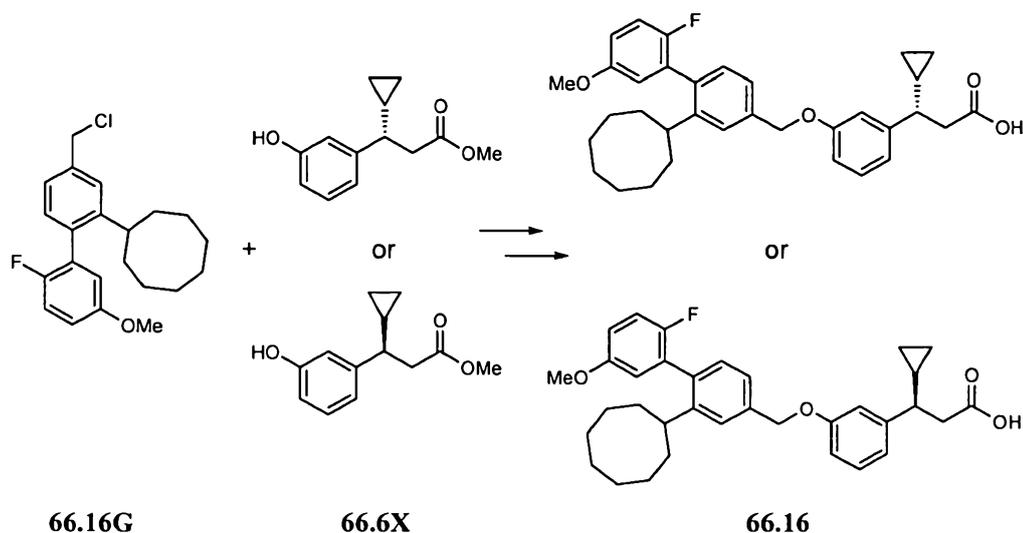
[0604] 2-(1-Cycloocten-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (66.16C). A mixture of triphenylphosphine (1 g, 4 mmol), potassium phenolate (7 g, 54 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (10 g, 39 mmol) and **66.16B** (10.00 g, 39 mmol) in toluene (194 mL) was degassed with nitrogen. Then, dichlorobis(triphenylphosphine)palladium(II) (1 g, 2 mmol) was added and the mixture was further degassed with nitrogen. The reaction mixture was stirred at 50°C for 3.5 hours. The reaction mixture was diluted with water and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-5% EtOAc in hexanes) to yield **66.16C** as a colorless oil (7.00 g, 77% yield).



[0607] (2-Cyclooctyl-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (**66.16F**). To a stirred solution of **66.16E** (0.387 g, 1 mmol) in EtOAc (11 mL) at 23°C was added palladium on carbon (0.1 g, 1 mmol). The reaction was placed under an atmosphere of hydrogen and stirred for 2 hours. The reaction mixture was then filtered and concentrated in vacuo. The residue was purified on silica gel (0-20% EtOAc in hexanes) to yield **66.16F** as a colorless oil (0.13 g, 33% yield).

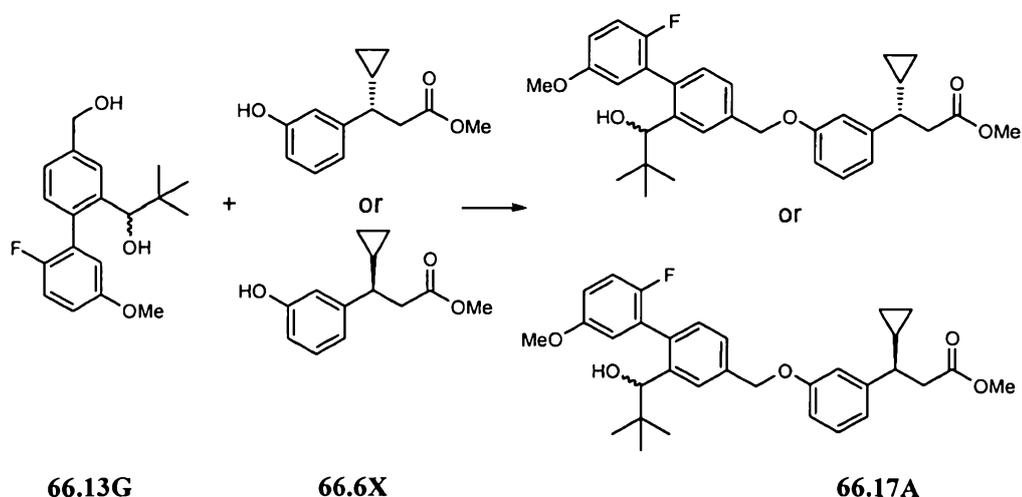


[0608] 4-(Chloromethyl)-2'-fluoro-5'-(methoxy)-2-cyclooctyl-1,1'-biphenyl (**66.16G**). To a stirred solution of **66.16F** (0.130 g, 0.4 mmol) in DCM (2.00 mL) and DMF (0.03 mL) at 0°C was added thionyl chloride (0.06 mL, 0.8 mmol). The reaction was stirred at room temperature for 2 hours. After which, the reaction was concentrated in vacuo and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.16G** as a colorless oil (0.130 g, 95% yield).



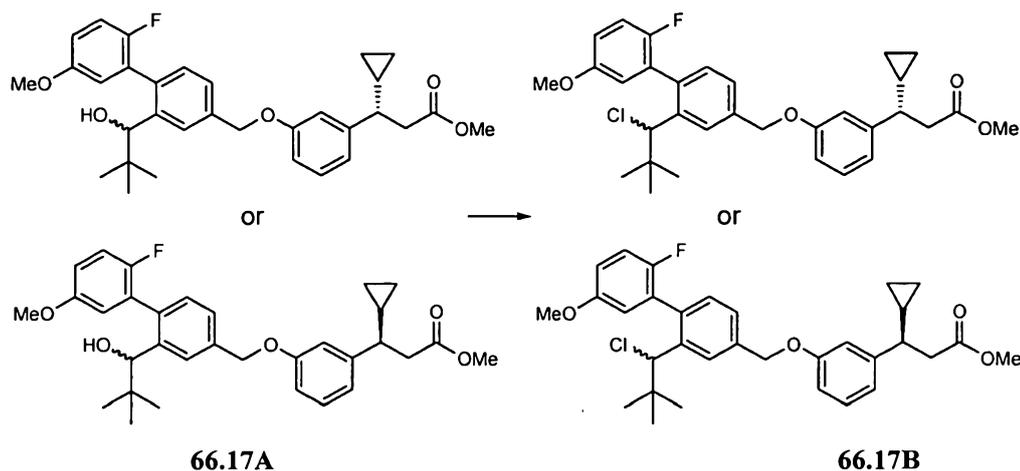
[0609] **(3S)-3-(3-(((2-Cyclooctyl-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclopropylpropanoic acid or (3R)-3-(3-(((2-cyclooctyl-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclopropylpropanoic acid (66.16).** The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (described herein) to yield 66.16 (0.0227 g, 63% yield over two steps). MS ESI (neg.) m/e: 529.3 (M-H)⁺.

[0610] **Example 66.17**

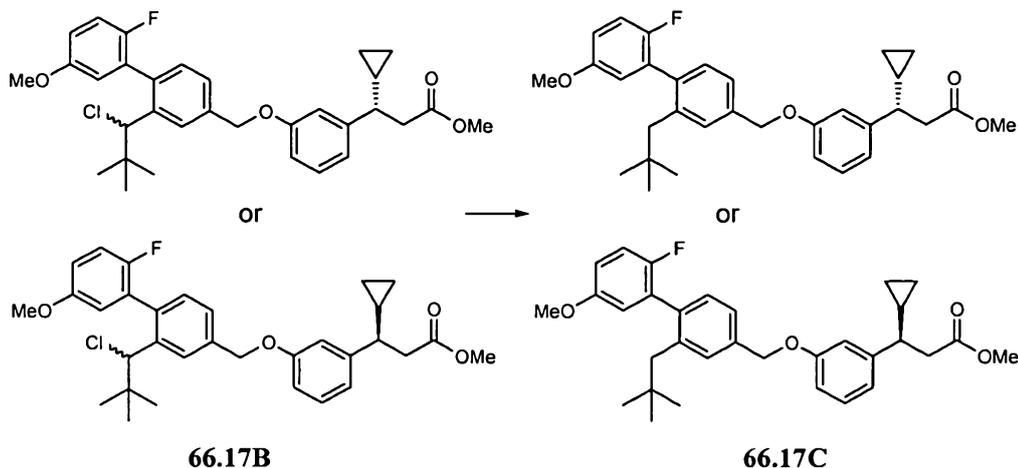


[0611] **Methyl (3S)-3-cyclopropyl-3-(3-(((2'-fluoro-2-(1-hydroxy-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2'-fluoro-2-(1-hydroxy-2,2-dimethylpropyl)-5'**

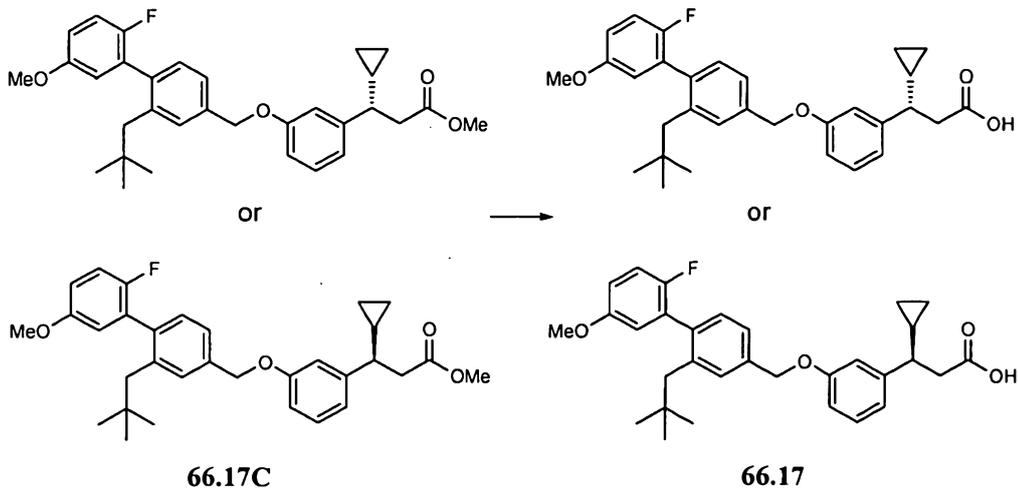
(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.17A). To a stirred solution of **66.6X** (0.730 g, 3.3 mmol) in THF (20.00 mL) at 23°C was added **66.13G** (1.1 g, 3.3 mmol), triphenylphosphine (1.3 g, 5.0 mmol), and then DEAD (0.79 mL, 5.0 mmol) over two hours. The reaction was further stirred for 21 hours, and then was diluted with water and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **66.17A** as a colorless oil (1.40 g, 81% yield).



[0612] Methyl (3S)-3-(3-(((2-(1-chloro-2,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclopropylpropanoate or methyl (3R)-3-(3-(((2-(1-chloro-2,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclopropylpropanoate (66.17B). To a stirred solution of **66.17A** (1.400 g, 2.7 mmol) in DCM (20.00 mL) at 23°C was added DMF (0.021 mL) followed by thionyl chloride (0.39 mL, 5.4 mmol). The reaction was stirred for 45 minutes, and then was concentrated in vacuo. The resulting product was purified on silica gel (0-10% EtOAc in hexanes) to yield **66.17B** as a colorless oil (1.300 g, 90% yield).



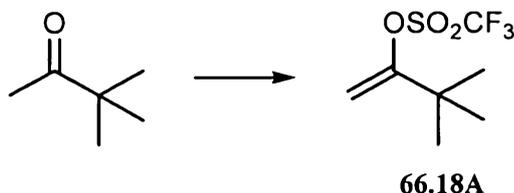
[0613] Methyl (3S)-3-cyclopropyl-3-(3-(((2-(2,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2-(2,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (**66.17C**). To a stirred solution of **66.17B** (1.30 g, 2.4 mmol) in toluene (10.00 mL) at 23°C was added AIBN (0.040 g, 0.24 mmol) followed by tri-n-butyltin hydride (1.9 mL, 7.2 mmol). The reaction mixture was heated to 100 °C and stirred for 1 hour. The reaction mixture was then concentrated in vacuo, and the residue was purified on silica gel (0-15% EtOAc in hexanes) to yield **66.17C** as a colorless oil (1.10 g, 90% yield).



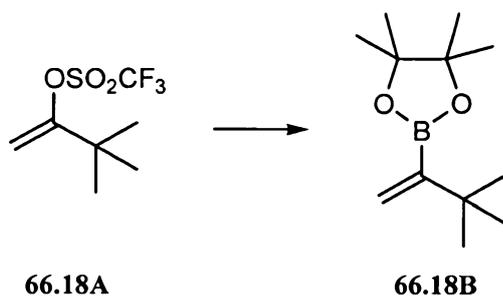
[0614] (3S)-3-Cyclopropyl-3-(3-(((2-(2,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-(2,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (**66.17**). The hydrolysis of **66.17C** was

conducted in an analogous manner to Example 66.6 (described herein) to yield 66.17 (0.900 g, 84%). MS ESI (neg.) m/e: 489.2 (M-H)⁺.

[0615] **Example 66.18**

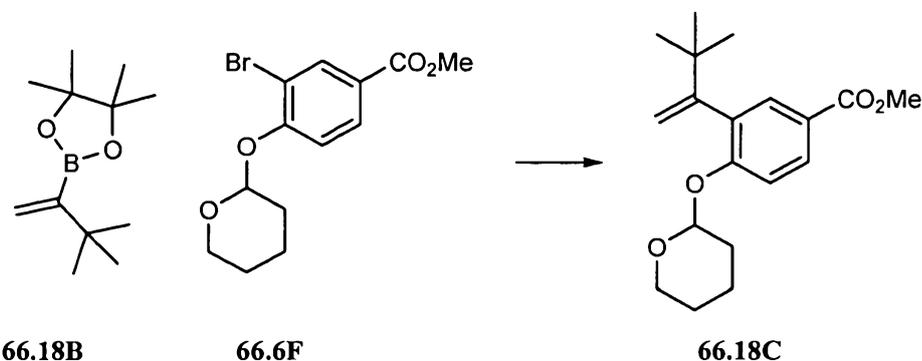


[0616] **Synthesis of 66.18A.** To a solution of 3,3-dimethylbutan-2-one (5.00 g, 50 mmol, commercially available from Aldrich) in THF (71 mL) at -78°C was added dropwise a solution of LDA (28 mL, 56 mmol). The resulting solution was stirred at -78°C for 20 minutes. A solution of N-phenyl-bis(trifluoromethane sulfonimide) (20 g, 55 mmol) in THF (15 mL) was then added slowly at -78°C. The reaction mixture was allowed to room temperature over 3 hours. The reaction was concentrated in vacuo. The reaction was then diluted with water and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was purified on silica gel (0-5% EtOAc in hexanes) to yield 66.18A as a colorless oil (10.00 g, 86% yield)

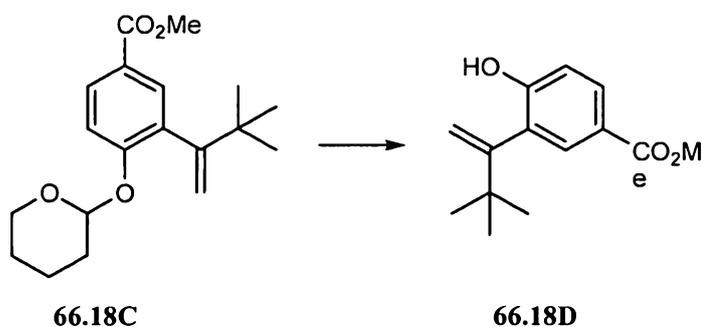


[0617] **Synthesis of 66.18B.** A mixture of triphenylphosphine (0.90 g, 3.4 mmol), potassium phenolate (6.4 g, 48 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (8.7 g, 34 mmol) and 66.18A (8.00 g, 34 mmol) in toluene (172 mL) was degassed by N₂. Then dichlorobis(triphenylphosphine)palladium(II) (1.2 g, 1.7 mmol) was added, and the reaction mixture was further degassed with N₂. The reaction was then stirred at 50°C for 3.5 hours. The reaction was then filtered and concentrated in vacuo. The product was

purified on silica gel (0-5% EtOAc in hexanes) to yield **66.18B** as a colorless oil (5.0 g, 69% yield).

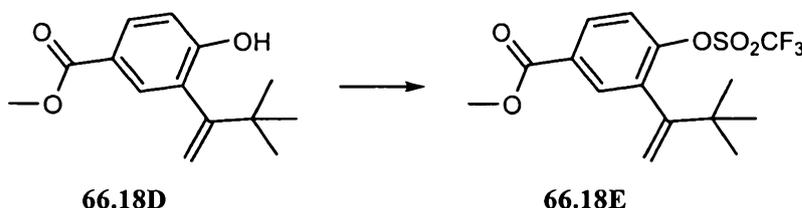


[0618] Methyl 3-(1-(1,1-dimethylethyl)ethenyl)-4-(tetrahydro-2H-pyran-2-yloxy)benzoate (66.18C). A stirred solution of methyl 3-bromo-4-(tetrahydro-2H-pyran-2-yloxy)benzoate **66.6F** (2.50 g, 7.9 mmol), palladium acetate (0.18 g, 0.79 mmol), S-Phos (0.65 g, 1.6 mmol), tripotassium phosphate (1.6 mL, 20 mmol) in DMF (15.00 mL, 194 mmol) and water (0.600 mL, 33 mmol) was purged 3 times with nitrogen and placed under vacuum and the process repeated three times. Before heating, **66.18B** (2.0 g, 9.5 mmol) was added, and the mixture was heated to 70°C and stirred for 19 hours. The resulting mixture was then cooled to room temperature, diluted with water and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **66.18C** as a colorless oil (2.50 g, 99% yield).

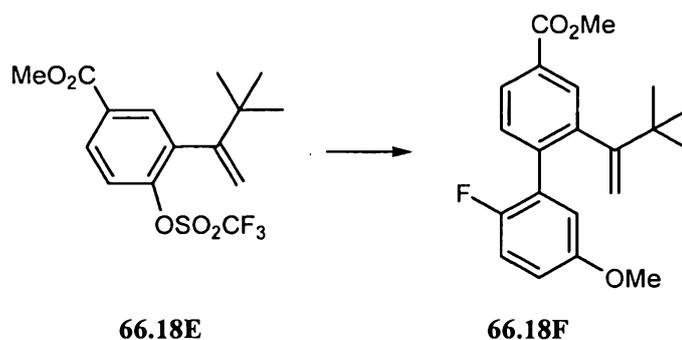


[0619] Methyl 3-(1-(1,1-dimethylethyl)ethenyl)-4-hydroxybenzoate (66.18D). To a stirred solution of **66.18C** (2.500 g, 7.85 mmol) in MeOH (10.00 mL, 7.85 mmol) at 23°C was added PPTS (0.197 g, 0.785 mmol). The reaction was heated to 60°C and

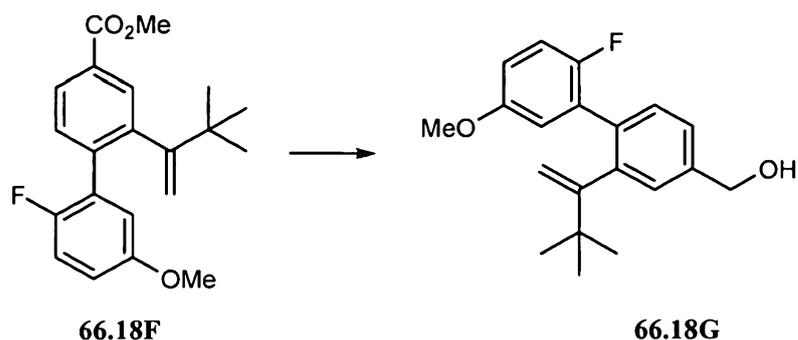
stirred for 19 hours. The reaction was then concentrated in vacuo to give a clear oil. The product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **66.18D** as a colorless oil (1.50 g, 81.5% yield).



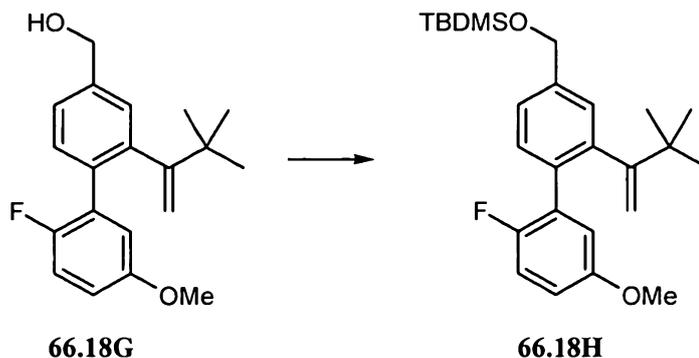
[0620] Methyl 3-(1-(1,1-dimethylethyl)ethenyl)-4-((trifluoromethyl)sulfonyl)oxybenzoate (66.18E). To a stirred solution of **66.18D** (0.500 g, 2 mmol) in DCM (11 mL) at 23°C was added TEA (0.4 mL, 3 mmol), DMAP (catalytic), and then N-phenyltriflimide (0.8 g, 2 mmol). The reaction was further stirred for 19 hours and then concentrated in vacuo. The product was purified on silica gel (0-10% EtOAc in hexanes) to yield **66.18E** as a colorless oil (0.1 g, 13% yield).



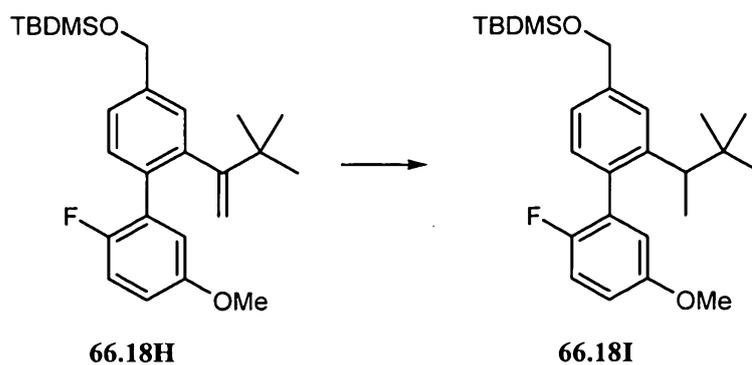
[0621] Methyl 2-(1-(1,1-dimethylethyl)ethenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.18F). To a stirred solution of **66.18E** (0.550 g, 1.5 mmol) in DMF (3.0 mL, 1.5 mmol) at 23°C was added 2-fluoro-5-methoxyphenylboronic acid (0.38 g, 2.3 mmol) (commercially available from Aldrich), potassium carbonate (0.62 g, 4.5 mmol) and then tetrakis(triphenylphosphine)palladium (0.12 g, 0.11 mmol). The mixture was heated to 90°C and stirred for 17 hours. The resulting mixture was then cooled to room temperature, diluted with water and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.18F** as a colorless oil (0.100 g, 19% yield).



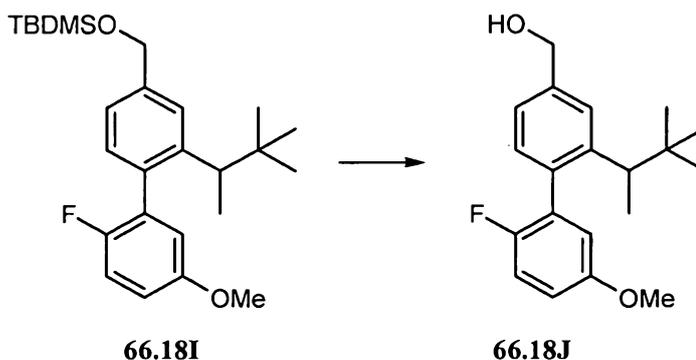
[0622] **(2-(1-(1,1-Dimethylethyl)ethenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (66.18G)**. To a stirred solution of **66.18F** (0.400 g, 1 mmol) in THF (6 mL) at 0°C was added LAH in THF (2 mL, 2 mmol, 1.0M). The resulting mixture was stirred for 2 hours. 1N NaOH(aq) was then added to the mixture, and the resulting mixture was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **66.18G** as a colorless oil (0.273 g, 74% yield).

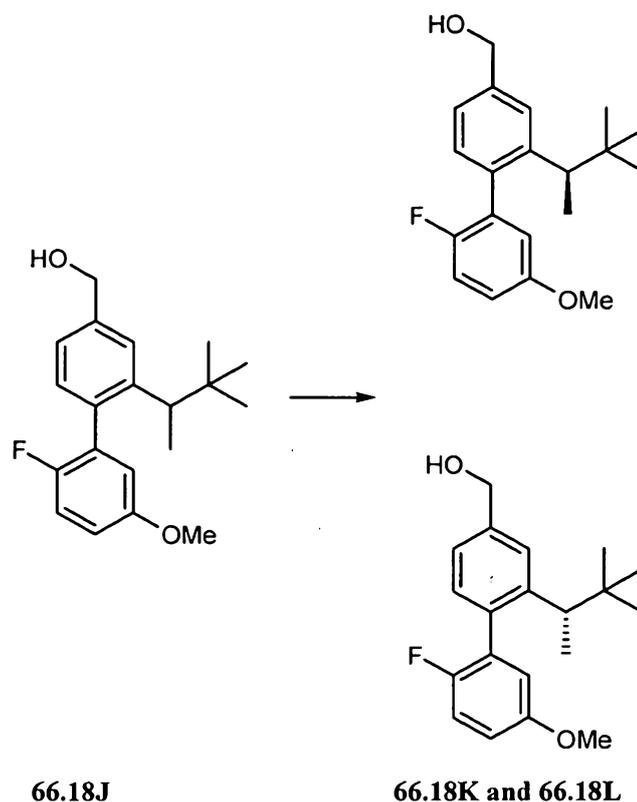


[0623] **(1,1-Dimethylethyl)((2-(1-(1,1-dimethylethyl)ethenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)dimethylsilane (66.18H)**. To a stirred solution of **66.18G** (0.273 g, 0.9 mmol) in DCM (2.00 mL) at 23°C was added tert-butyldimethylsilyl chloride (0.2 mL, 1 mmol), followed by TEA (0.1 mL, 1 mmol) and DMAP (0.01 g, 0.09 mmol). The resulting mixture was then stirred for 16 hours and then was concentrated in vacuo to give the product. The product was purified on silica gel (0-5% EtOAc in hexanes) to yield **66.18H** as a colorless oil (0.374 g, 100% yield).

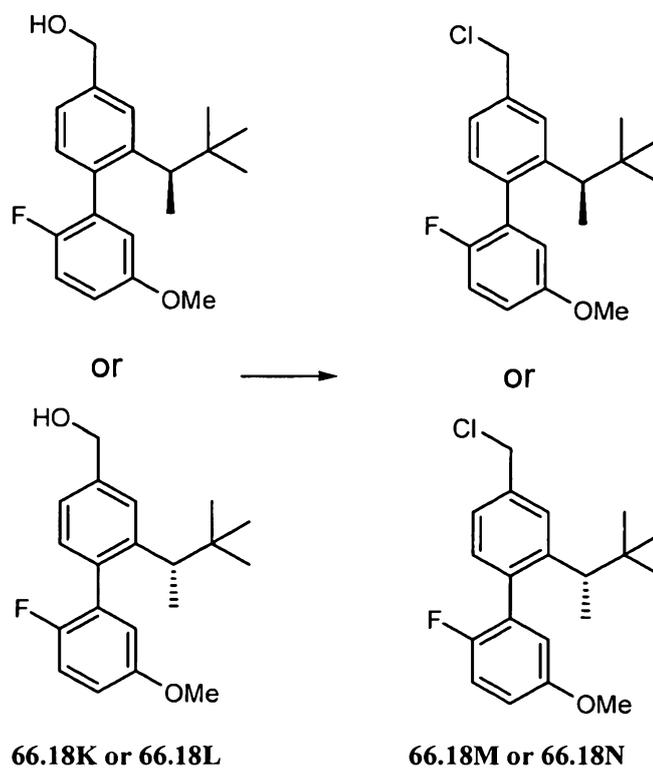


[0624] **(1,1-Dimethylethyl)((2'-fluoro-5'-(methoxy)-2-(1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxydimethylsilane (66.18I)**. To a stirred solution of **66.18H** (0.400 g, 0.93 mmol) in EtOAc (2.00 mL) at 23°C was added palladium on carbon (0.0099 g, 0.093 mmol). The resulting mixture was stirred under an atmosphere of hydrogen for 21 hours and then was filtered and concentrated in vacuo. The product was purified on silica gel (0-5% EtOAc in hexanes) to yield **66.18I** as a colorless oil (0.400 g, 100% yield).

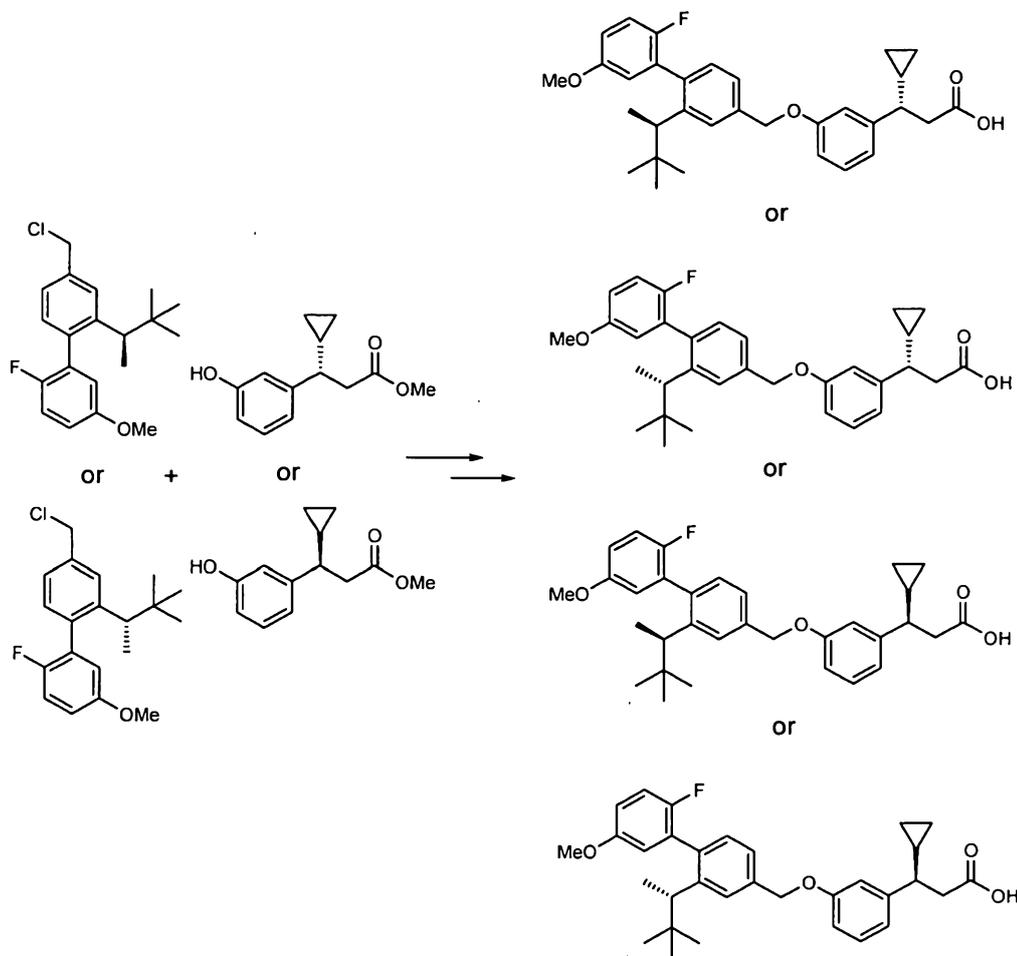




[0625] (2'-Fluoro-5'-(methoxy)-2-((1R)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methanol and (2'-fluoro-5'-(methoxy)-2-((1S)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methanol (66.18K and 66.18L). To a stirred solution of 66.18J (0.400 g, 0.929 mmol) in MeOH (10.00 mL, 0.929 mmol) at 23°C was added PPTS (0.0233 g, 0.0929 mmol). The mixture was stirred for 19 hours and then was concentrated in vacuo to give a clear oil. The product was then purified on silica gel (0-20% EtOAc in hexanes) to yield 66.16J as a colorless oil (0.250 g, 85% yield). Chiral separation of 66.18J was accomplished on Chiracel-OD (3%IPA in hexane) to provide 66.18K (peak one) and 66.18L (peak two). Both enantiomers were used to synthesize example compounds, and both enantiomers gave active example compounds. However, the enantiomer corresponding to peak 2 provided the most active example compounds. ¹



[0626] 4-(Chloromethyl)-2'-fluoro-5'-(methoxy)-2-((1R)-1,2,2-trimethylpropyl)-1,1'-biphenyl or 4-(chloromethyl)-2'-fluoro-5'-(methoxy)-2-((1S)-1,2,2-trimethylpropyl)-1,1'-biphenyl (**66.18M or 66.18N**). To a stirred solution of **66.18K or 66.18L** (0.050 g, 0.16 mmol) in DCM (2.00 mL) at 23°C was added DMF (0.0012 mL) followed by thionyl chloride (0.023 mL, 0.32 mmol). The mixture was stirred for one hour and then was concentrated in vacuo. The resulting product was purified on silica gel (0-10% EtOAc in hexanes) to yield **66.18M or 66.18N** as a colorless oil (0.050 g, 94% yield).



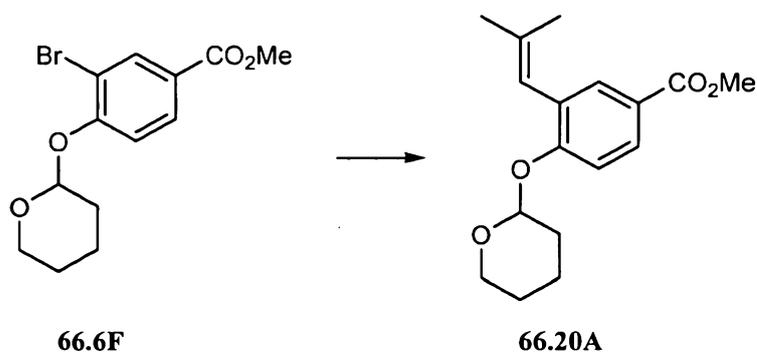
66.18M or 66.18N 66.6X

66.18O or 66.18P

[0627] (3S)-3-Cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-((1R)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-((1S)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-((1R)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-((1S)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.18). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using the chloromethyl compound derived from peak one from the chiral separation of 66.18J on the OD-column, described herein) to yield 66.18 (0.0334 g, 73% yield over the two steps). MS ESI (neg.) m/e: 503.2 (M-H)⁺.

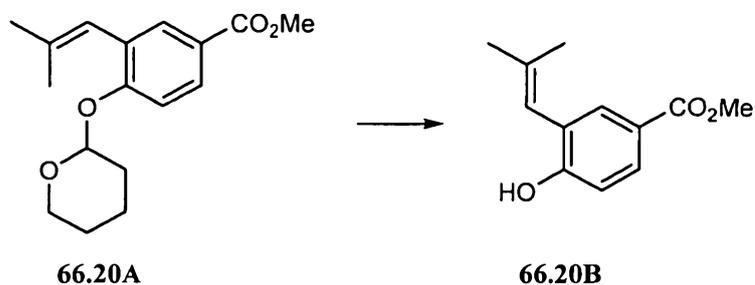
[0628] (3S)-3-cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-((1R)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-((1S)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-((1R)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-((1S)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.19). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using the chloromethyl compound derived from peak two from the chiral separation of 66.18J on the OD-column, described herein) to yield 66.19A or 66.19B (0.0305 g, 66% yield over two steps). MS ESI (neg.) m/e: 503.2 (M-H)⁺.

[0629] **Example 66.20**

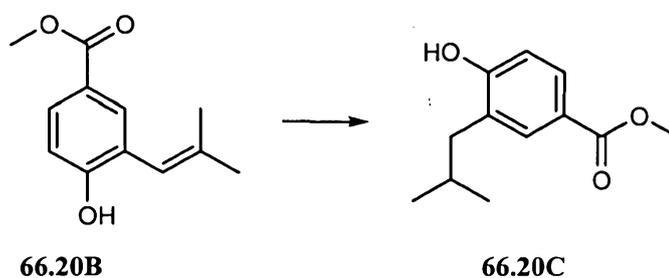


[0630] **Methyl 3-(2-methyl-1-propenyl)-4-(tetrahydro-2H-pyran-2-yloxy)benzoate (66.20A).** A mixture of methyl 3-bromo-4-(tetrahydro-2H-pyran-2-yloxy)benzoate 66.6F (0.500 g, 1.6 mmol), palladium acetate (0.036 g, 0.16 mmol), S-Phos (0.13 g, 0.32 mmol) and tripotassium phosphate (0.32 mL, 4.0 mmol) in DMF (10.00 mL, 129 mmol) and water (0.40 mL, 22 mmol) was stirred. The mixture was purged with nitrogen and placed under vacuum and the process repeated three times. Before heating, 2-methylprop-1-enylboronic acid (0.24 g, 2.4 mmol, commercially available from Synthonix, Cat. No. D3007G1) was added, and the mixture was heated to 70°C and stirred for 23 hours. The mixture was then cooled to room temperature, diluted with brine, and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure

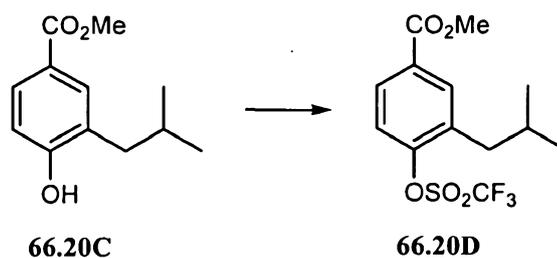
and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.20A** as a colorless oil (0.460 g, 100% yield).



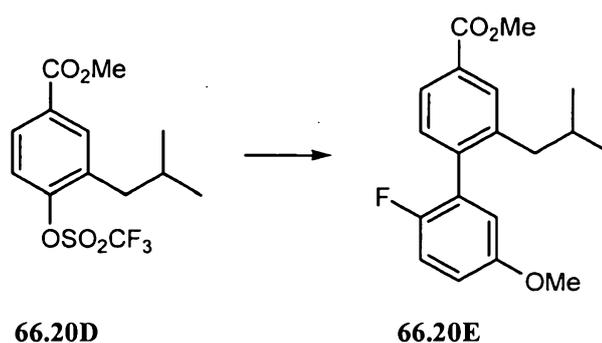
[0631] Methyl 4-hydroxy-3-(2-methyl-1-propenyl)benzoate (66.20B). To a stirred mixture of **66.20A** (0.460 g, 2 mmol) in MeOH (8 mL) was added PPTS (0.04 g, 0.2 mmol). The reaction mixture was then stirred for 24 hours and then concentrated in vacuo. The residue was purified on silica gel (0-20% EtOAc in hexanes) to yield **66.20B** as a colorless oil (0.320 g, 98% yield).



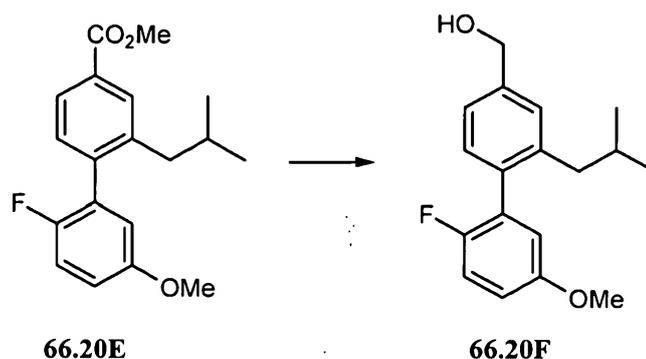
[0632] Methyl 4-hydroxy-3-(2-methylpropyl)benzoate (66.20C). To a stirred solution of methyl 4-hydroxy-3-(2-methylprop-1-enyl)benzoate **66.20B** (0.320 g, 1.6 mmol) in EtOAc (2.00 mL, 20 mmol) at 23°C was added palladium on carbon (0.017 g, 0.16 mmol). The reaction was stirred under an atmosphere of hydrogen (0.0031 g, 1.6 mmol) for 16 hours. The reaction mixture was then filtered and concentrated in vacuo to give a clear oil. The residue was purified on silica gel (0-20% EtOAc in hexanes) to yield **66.20C** as a colorless oil (0.256 g, 79% yield)



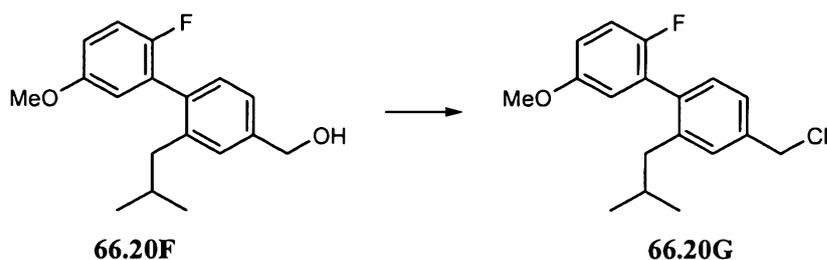
[0633] **Methyl 3-(2-methylpropyl)-4-(((trifluoromethyl)sulfonyl)oxy)benzoate (66.20D)**. To a stirred solution of **66.20C** (0.256 g, 1 mmol) in DCM (12 mL, 1 mmol) at 0°C was added TEA (0.2 mL, 1 mmol), and a catalytic amount of DMAP. N-phenyltriflimide (0.5 g, 1 mmol) was then added and the mixture was stirred at room temperature for 20 hours. The reaction was concentrated in vacuo, and the residue was purified on silica gel (0-10% EtOAc in hexanes) to yield **66.20D** as a colorless oil (0.400 g, 96% yield).



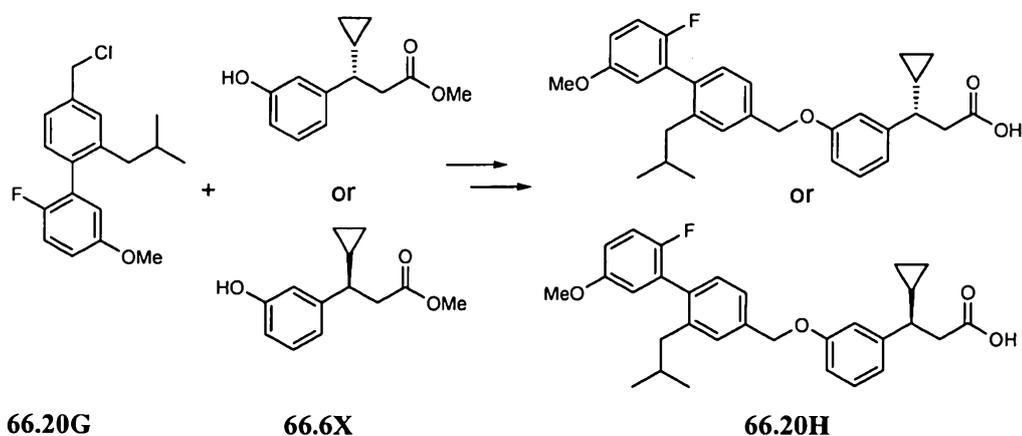
[0634] **Methyl 2'-fluoro-5'-(methoxy)-2-(2-methylpropyl)-1,1'-biphenyl-4-carboxylate (66.20E)**. To a stirred solution of **66.20D** (0.400 g, 1.2 mmol) in DMF (4.00 mL, 52 mmol) at 23°C was added 2-fluoro-5-methoxyphenylboronic acid (0.40 g, 2.4 mmol)(commercially available from Aldrich), potassium carbonate (0.49 g, 3.5 mmol), and then tetrakis(triphenylphosphine)palladium (0.14 g, 0.12 mmol). The mixture was heated to 90 °C and stirred for 22 hours. The mixture was cooled to room temperature, diluted with brine, and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.20E** as a colorless oil (0.293 g, 79% yield).



[0635] **(2'-Fluoro-5'-(methoxy)-2-(2-methylpropyl)-1,1'-biphenyl-4-yl)methanol (66.20E)**. To a stirred solution of **66.20E** (0.293 g, 0.9 mmol) in THF (5 mL, 0.9 mmol) at 0°C was added LAH in THF (2 mL, 2 mmol, 1.0M). The reaction was stirred for one hour and then 1N NaOH(aq) was added to quench the mixture. The reaction was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **66.20F** as a colorless oil (0.260 g, 97% yield).

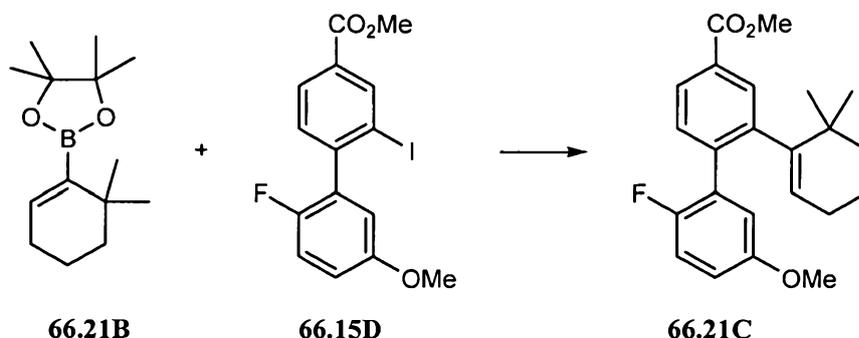


[0636] **4-(Chloromethyl)-2'-fluoro-5-(methoxy)-2-(2-methylpropyl)-1,1'-biphenyl 66.20G**. To a stirred solution of **66.20F** (0.260 g, 0.90 mmol) in DCM (2.00 mL, 31 mmol) at 23°C was added DMF (0.0070 mL, 0.090 mmol) followed by thionyl chloride (0.13 mL, 1.8 mmol). The reaction was stirred for one hour and then the reaction was concentrated in vacuo. The residue was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.20G** as a colorless oil (0.252 g, 91% yield).

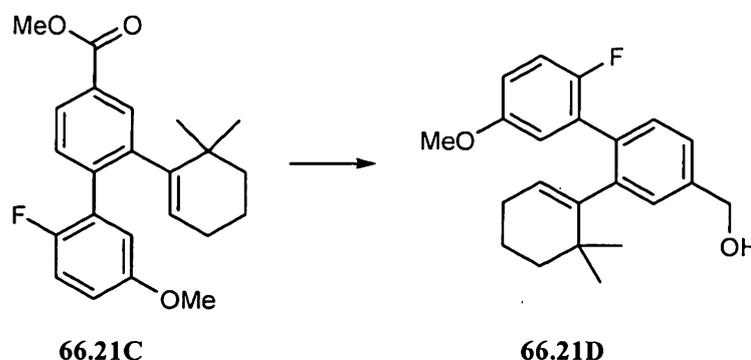


[0637] **(3S)-3-Cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-(2-methylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-**

and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.21B** as a colorless oil (3.00 g, 80% yield).

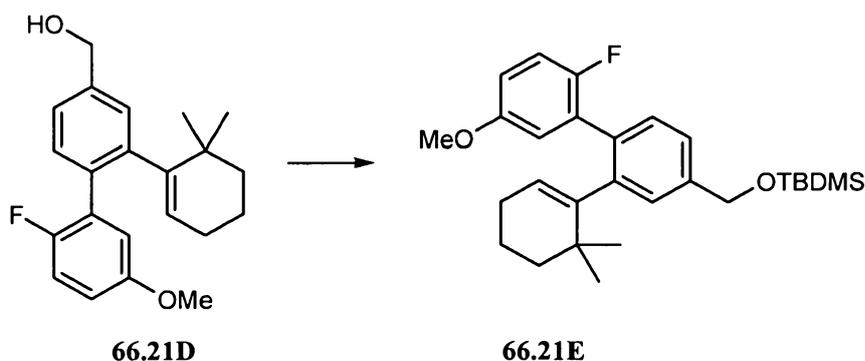


[0641] **Methyl 2-(6,6-dimethyl-1-cyclohexen-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.21C)**. To a stirred solution of **66.15D** (0.750 g, 1.9 mmol) in DMF (4.00 mL, 52 mmol) at 23°C was added **66.21B** (0.92 g, 3.9 mmol), potassium carbonate (0.81 g, 5.8 mmol), and then tetrakis(triphenylphosphine)palladium (0.22 g, 0.19 mmol). The mixture was heated to 90°C and stirred for 24 hours. The reaction was then cooled to room temperature, diluted with brine, and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.21C** as a colorless oil (0.34 g, 48% yield).

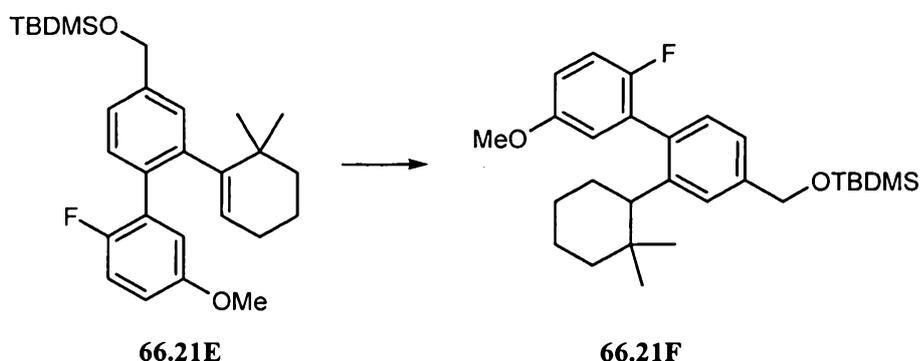


[0642] **(2-(6,6-Dimethyl-1-cyclohexen-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (66.21D)**. To a stirred solution of **66.21C** (0.300 g, 0.814

mmol) in THF (0.0587 g, 0.814 mmol) at 0°C was added LAH in THF (1.63 mL, 1.63 mmol, 1.0M). The reaction was stirred for 4.5 hours and then 1N NaOH(aq) was added to quench the mixture. The reaction was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **66.21D** as a colorless oil (0.250 g, 90.2% yield).

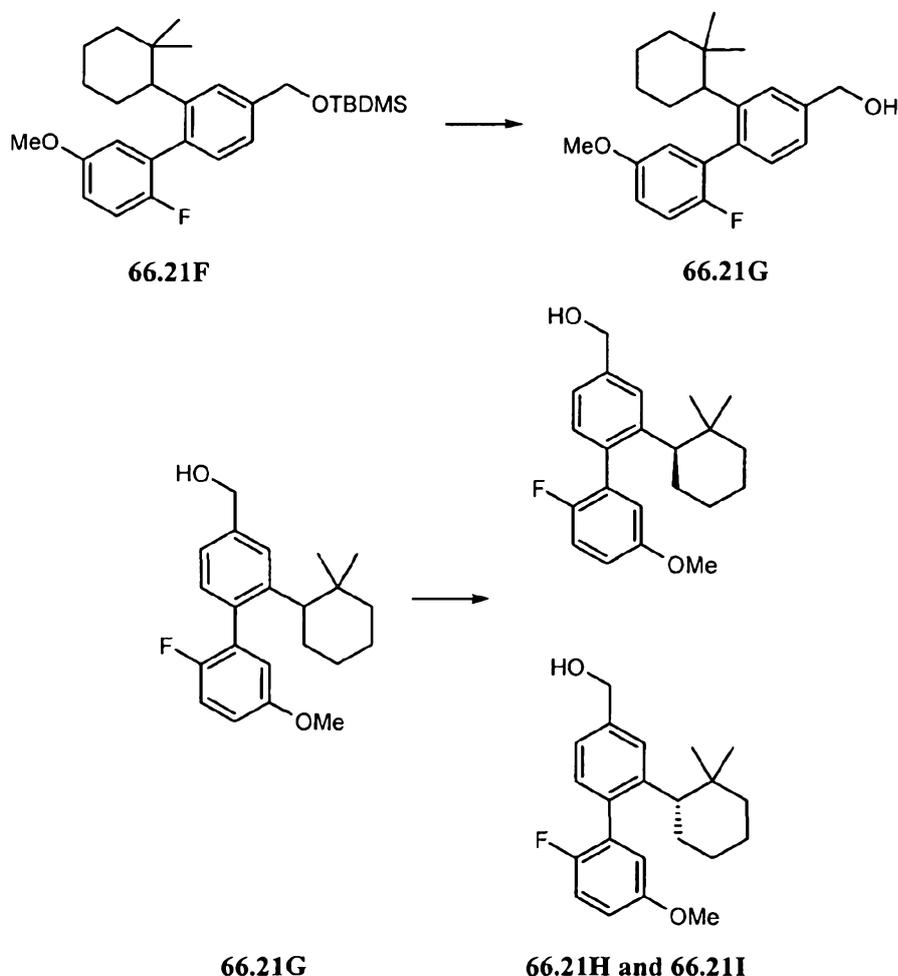


[0643] **(((2-(6,6-Dimethyl-1-cyclohexen-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)(1,1-dimethylethyl)dimethylsilane (66.21E).** To a stirred solution of **66.21D** (0.160 g, 0.5 mmol) in DCM (10.00 mL, 155 mmol) at 23°C was added tert-butyldimethylsilyl chloride (0.09 mL, 0.6 mmol), followed by TEA (0.08 mL, 0.6 mmol) and DMAP (0.006 g, 0.05 mmol). The reaction was stirred for one hour and then concentrated in vacuo. The crude product was then purified on silica gel (0-5% EtOAc in hexanes) to yield **66.21E** as a colorless oil (0.198 g, 93% yield).

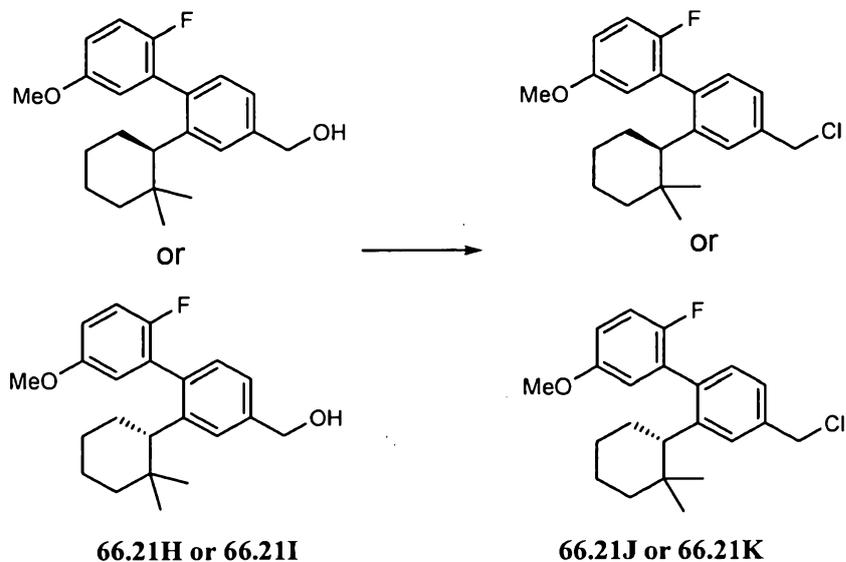


[0644] **Synthesis of 66.21F.** To a stirred solution of **66.21E** (0.090 g, 0.20 mmol) in EtOAc (2.00 mL, 20 mmol) at 23°C was added palladium on carbon (0.0021 g, 0.020 mmol). The resulting mixture was stirred under an atmosphere of hydrogen for 4

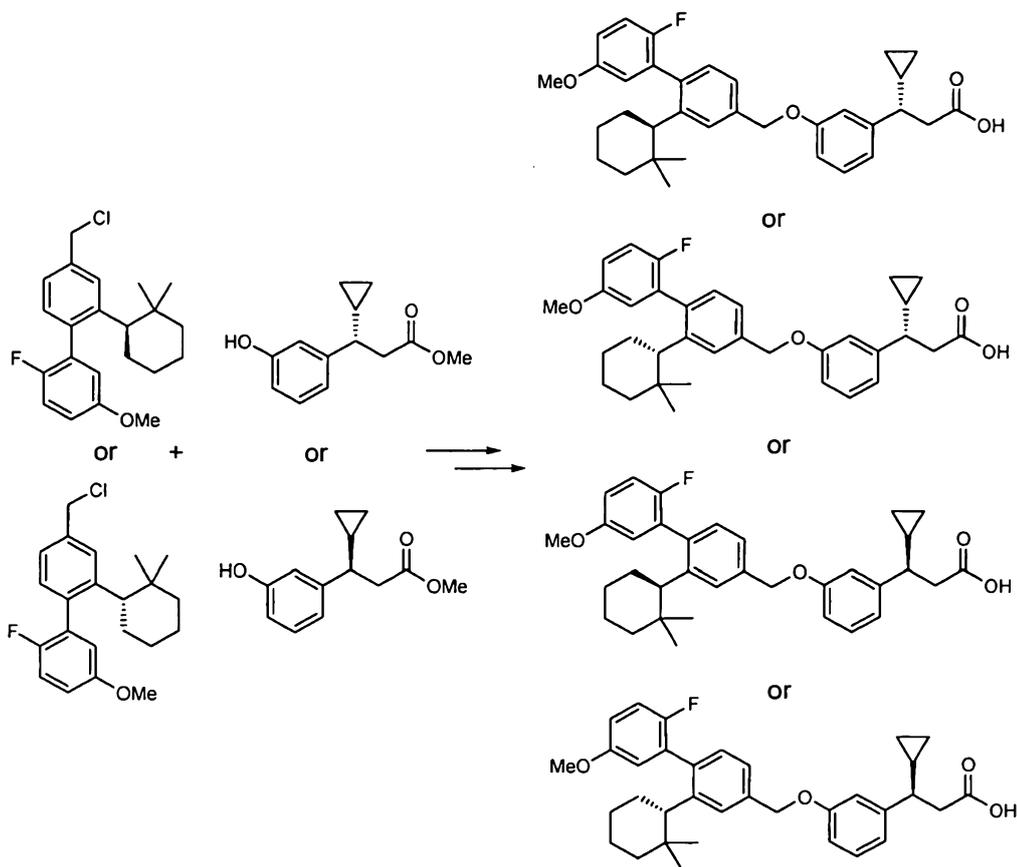
days. The reaction mixture was filtered, and the filtrate was concentrated in vacuo to yield **66.21F** as a colorless oil (0.090 g, 100% yield)



[0645] (2-((1R)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol and (2-((1S)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (**66.21H** and **66.21I**). To a stirred mixture of **66.21F** (0.090 g, 0.20 mmol) in MeOH (0.99 mL, 0.20 mmol) was added PPTS (0.0050 g, 0.020 mmol). The resulting mixture was stirred for 4.5 hours and then was concentrated in vacuo. The residue was purified on silica gel (0-15% EtOAc in hexanes) to yield a colorless oil (0.067 g, 99% yield). Chiral separation of **66.21G** was accomplished on Chiracel-OD (3%IPA in hexane) to provide **66.21H** (peak one) and **66.21I** (peak two). Both enantiomers were used to synthesize example compounds, and both enantiomers gave active example compounds. However, the enantiomer corresponding to peak 2 provided the most active example compounds. ¹



[0646] **4-(Chloromethyl)-2-((1R)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (66.21 J or 66.21K).** To a stirred solution of **66.21H or 66.21I** (0.035 g, 0.10 mmol) in DCM (2.00 mL, 31 mmol) at 23°C was added DMF (0.00079 mL, 0.010 mmol) followed by thionyl chloride (0.015 mL, 0.20 mmol). The reaction was stirred for one hour. After which, the reaction mixture was concentrated in vacuo. The crude product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.21J or 66.12K** as a colorless oil (0.025 g, 68% yield).



66.21J or 66.21K

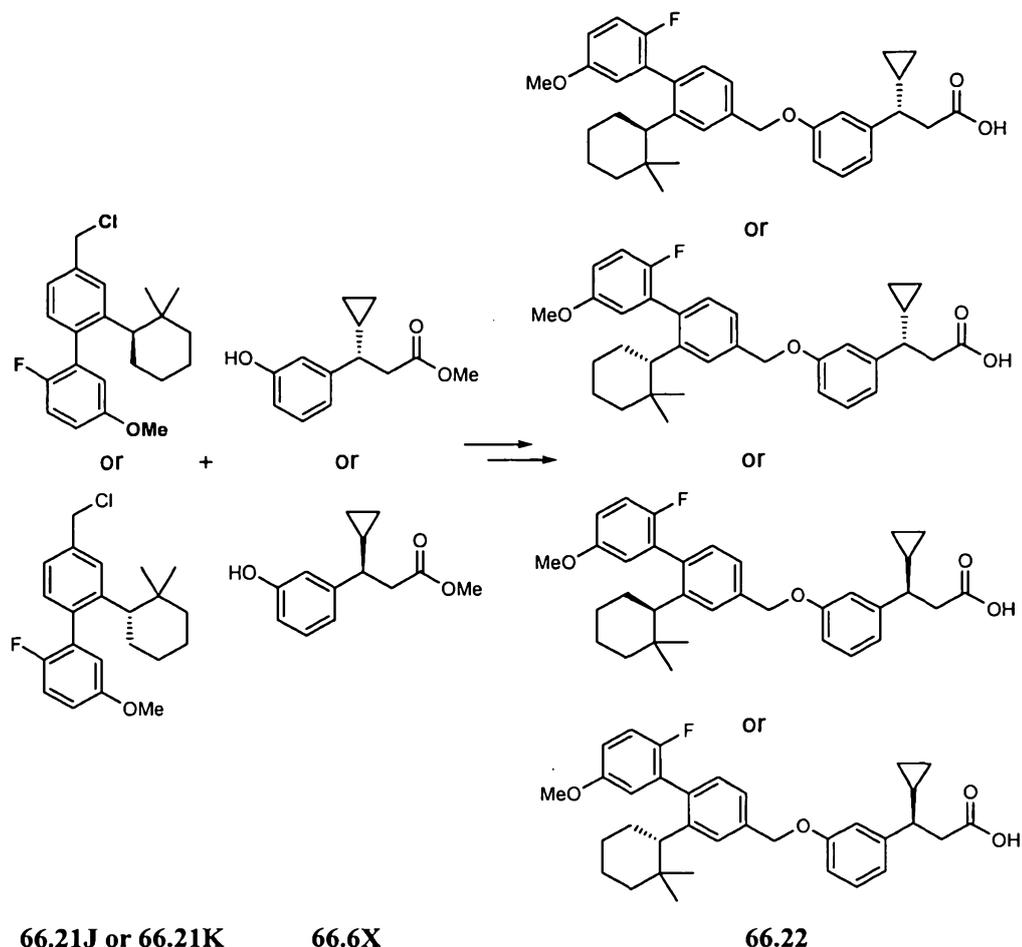
66.6X

66.21

[0647] (3S)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.21). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using peak one from the chiral separation of 66.21G on the OD-column, described herein) to yield 66.21 (0.0305 g, 10% yield over two steps). MS ESI (neg.) m/e: 529.3 (M-H)⁺.

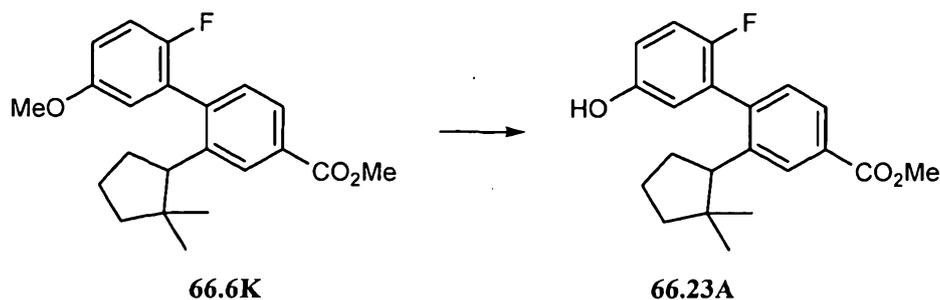
[0648]

Example 66.22

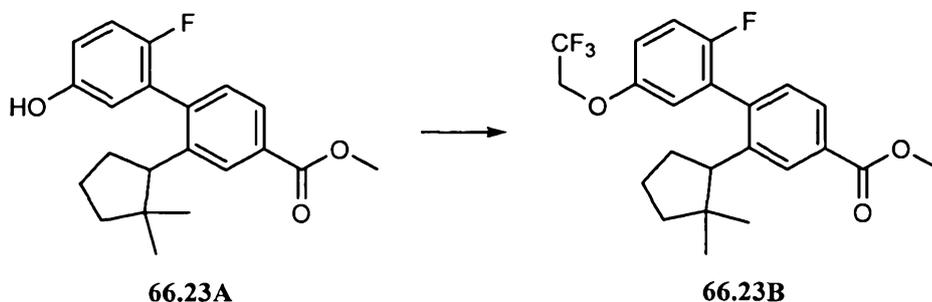


[0649] **(3S)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid 66.22.** The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using peak two from the chiral separation of 66.21G on the OD-column, described herein) to yield 66.22 (0.0151 g, 39% yield over two steps). MS ESI (neg.) m/e: 529.3 (M-H)⁺.

[0650] **Example 66.23**

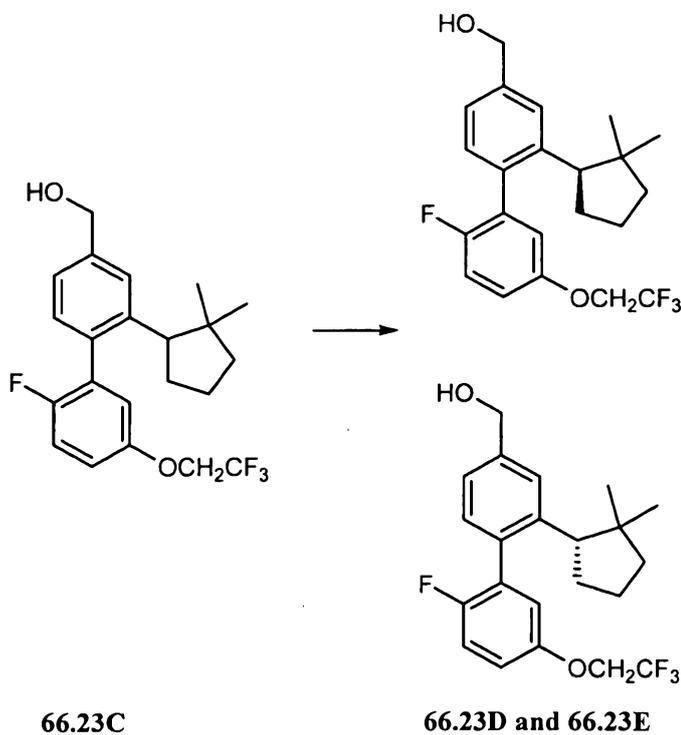
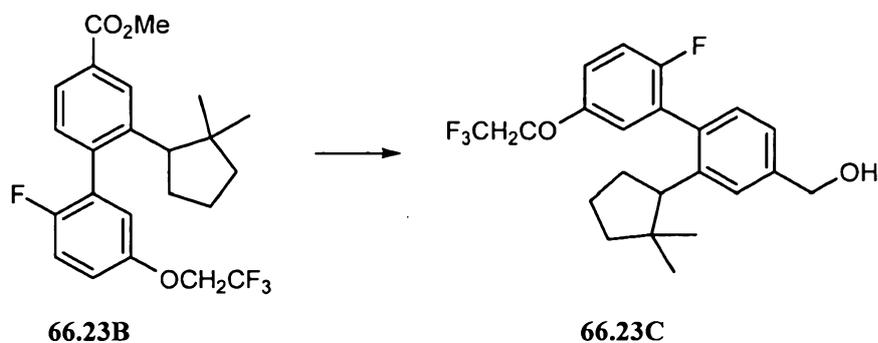


[0651] **Methyl 2-(2,2-dimethylcyclopentyl)-2'-fluoro-5'-hydroxy-1,1'-biphenyl-4-carboxylate (66.23A)**. To a stirred solution of **66.6K** (0.400 g, 1.12 mmol) in DCM (10.00 mL) at 0°C was added boron tribromide (1.0M in DCM)(4.49 mL, 4.49 mmol). The reaction was stirred for one hour at 0°C. Water was then added, and the mixture was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the desired product was isolated. The initial product was dissolved in a 1/1 mixture of THF/ethanol and to this was added 1N NaOH (aq), the resulting solution was stirred for 16 hours, after which it was concentrated in vacuo. The reaction was acidified with 1N HCl and the resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure. The resulting product was dissolved in MeOH and a drop of sulfuric acid was added. The mixture was heated at 70°C for 16 hours. The reaction mixture was then concentrated in vacuo. The product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **66.23A** as a colorless oil (0.250 g, 65% yield).



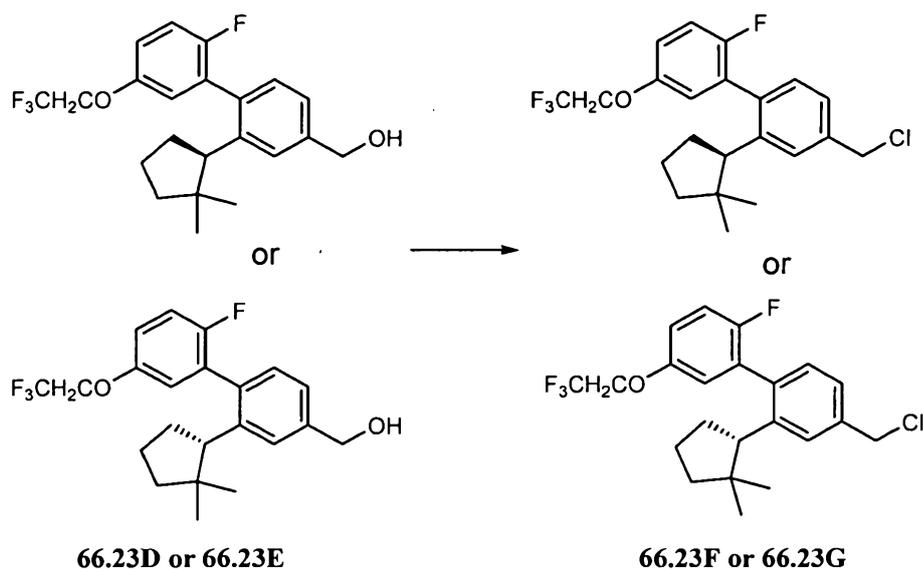
[0652] **Methyl 2-(2,2-dimethylcyclopentyl)-2'-fluoro-5'-((2,2,2-trifluoroethyl)oxy)-1,1'-biphenyl-4-carboxylate (66.23B)**. To a flask containing **66.23A** (0.100 g, 0.29 mmol) and cesium carbonate (0.29 g, 0.88 mmol) in DMF (2 mL) was added 1,1,1-trifluoro-2-iodoethane (0.12 g, 0.58 mmol)(commercially available from

Aldrich), and stirring was continued for 5 hours. The reaction was diluted with water and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.23B** as a colorless oil (0.113 g, 91% yield).

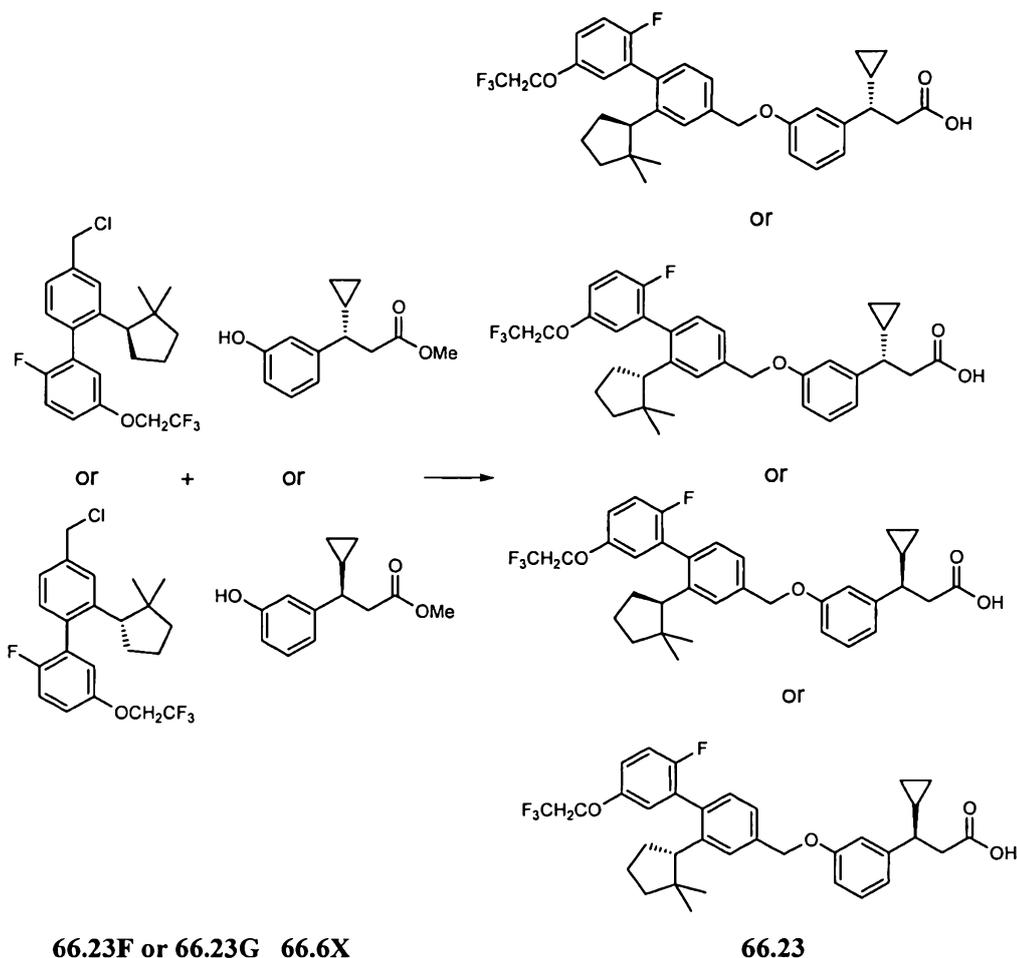


[0653] (2-((1R)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-((2,2,2-trifluoroethyl)oxy)-1,1'-biphenyl-4-yl)methanol and (2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-((2,2,2-trifluoroethyl)oxy)-1,1'-biphenyl-4-yl)methanol (**66.23D** and **66.23E**). To a stirred solution of **66.23B** (0.113 g, 0.3 mmol) in THF (5 mL) at 0°C was added LAH in THF (0.5 mL, 0.5 mmol, 1.0M). The mixture was stirred for one hour and then 1N NaOH(aq) was added to quench the reaction. The

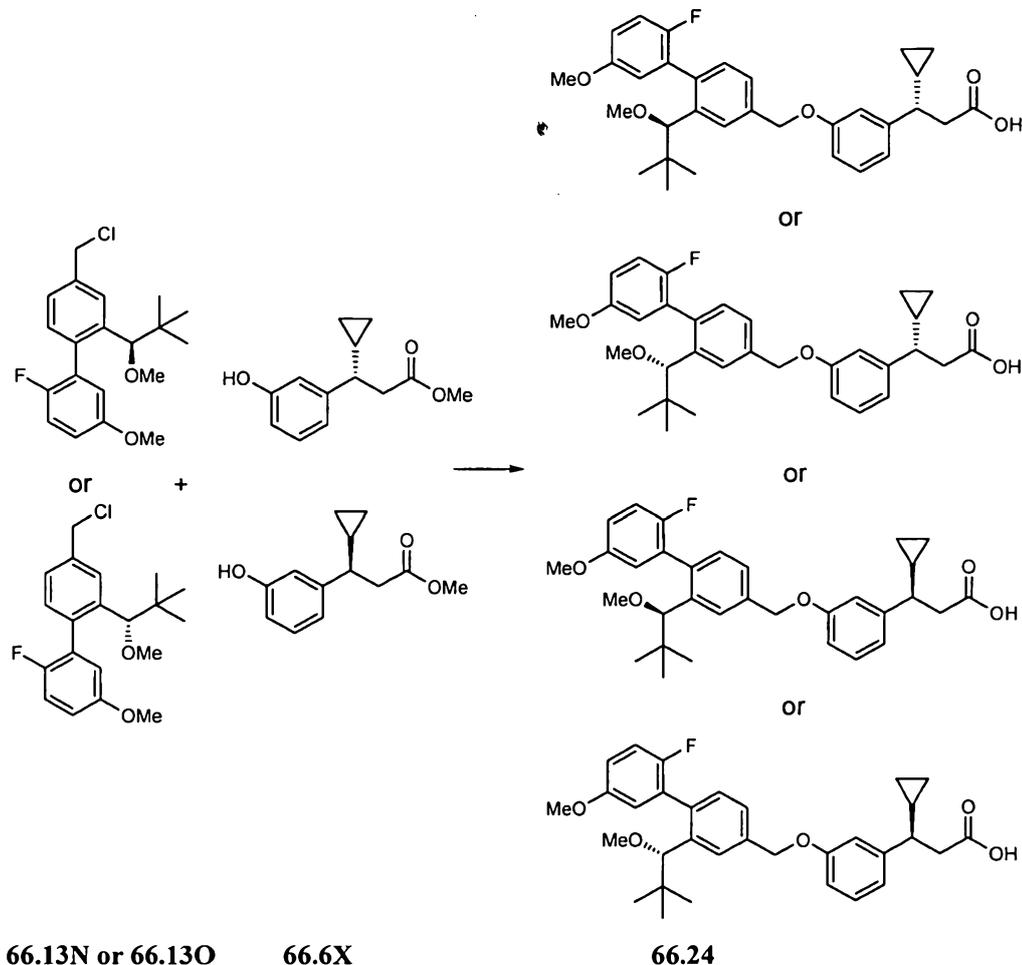
reaction mixture was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **66.23C** as a colorless oil (0.075 g, 71% yield). Chiral separation of **66.23C** was accomplished on Chiracel-OD (3%IPA in hexane) to provide **66.23D** (peak one) and **66.23E** (peak two). Both enantiomers were used to synthesize example compounds, and both enantiomers gave active example compounds. However, the enantiomer corresponding to peak 2 provided the most active example compounds. ¹



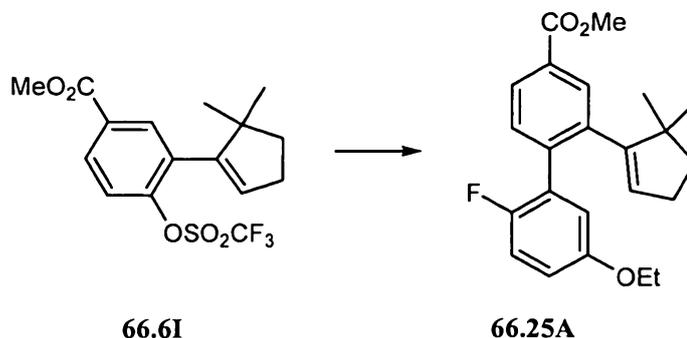
[0654] **4-(Chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-((2,2,2-trifluoroethyl)oxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-((2,2,2-trifluoroethyl)oxy)-1,1'-biphenyl (**66.23F or 66.23G**)**. To a stirred solution of **66.23D or 66.23E** (0.022 g, 0.055 mmol) in DCM (2.00 mL) at 23°C was added DMF (0.00043 mL) followed by thionyl chloride (0.0081 mL, 0.11 mmol). The reaction was stirred for two hours and then the reaction mixture was concentrated in vacuo. The product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.23F or 66.23G** as a colorless oil (0.019 g, 83% yield).



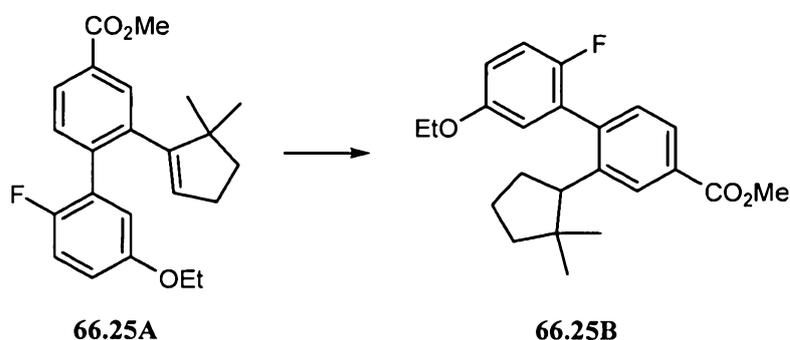
[0655] (3S)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-((2,2,2-trifluoroethyl)oxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-((2,2,2-trifluoroethyl)oxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-((2,2,2-trifluoroethyl)oxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-((2,2,2-trifluoroethyl)oxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.23H or 66.23I). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using the compound derived from peak two from the chiral separation of 66.23C on the OD-column, described herein) to yield 66.23 (0.011 g, 41% yield over two steps). MS ESI (neg.) m/e: 583.3 (M-H)⁺.

[0656] Example 66.24

[0657] (3S)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (**66.24**). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using the chloromethyl compound derived from peak one from the chiral separation of **66.13G** on the OD-column, described herein) to yield **66.24** (0.0332 g, 70% yield). MS ESI (neg.) m/e: 519.2 (M-H)⁺.

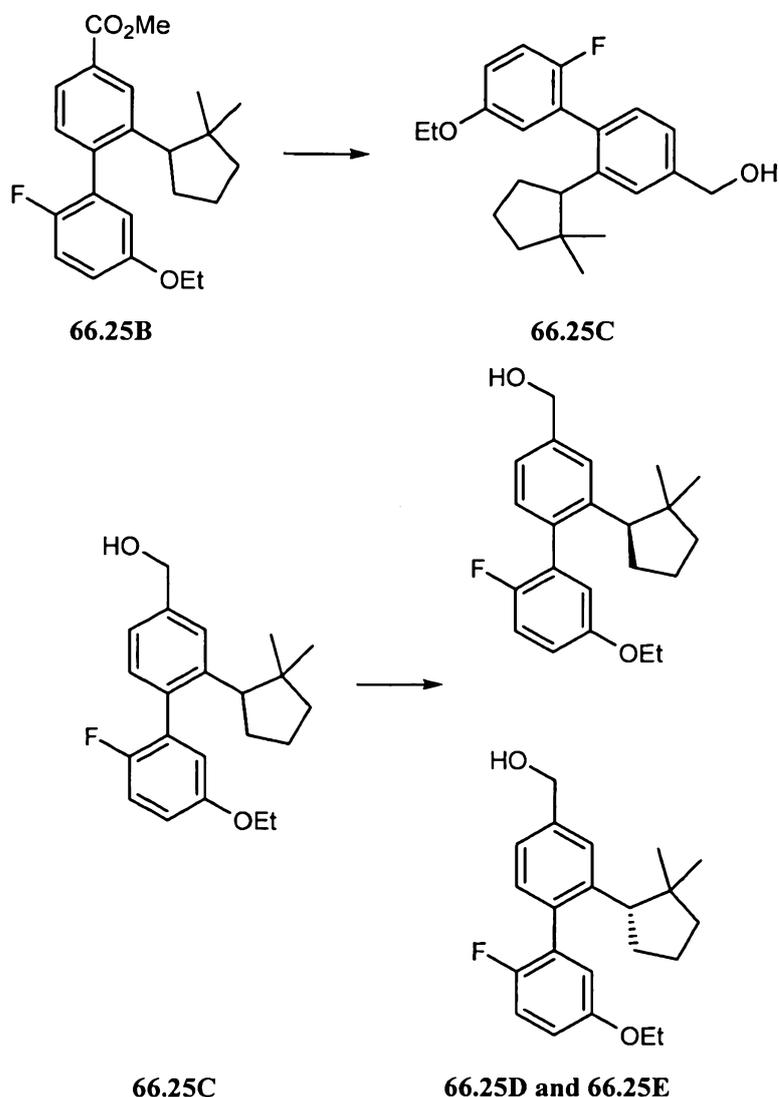
[0658] Example 66.25

[0659] Methyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-5'-(ethoxy)-2'-fluoro-1,1'-biphenyl-4-carboxylate (66.25A). To a stirred solution of methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-(trifluoromethylsulfonyloxy)benzoate **66.6I** (0.400 g, 1.1 mmol) in DMF (4.00 mL) at 23°C was added 5-ethoxy-2-fluorophenylboronic acid (0.29 g, 1.6 mmol, commercially available from Aldrich), potassium carbonate (0.44 g, 3.2 mmol), and then tetrakis(triphenylphosphine)palladium (0.12 g, 0.11 mmol). The mixture was heated to 90°C and stirred for 21 hours. The mixture was then cooled to room temperature, diluted with brine, and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.25A** as a colorless oil (0.350 g, 90% yield).



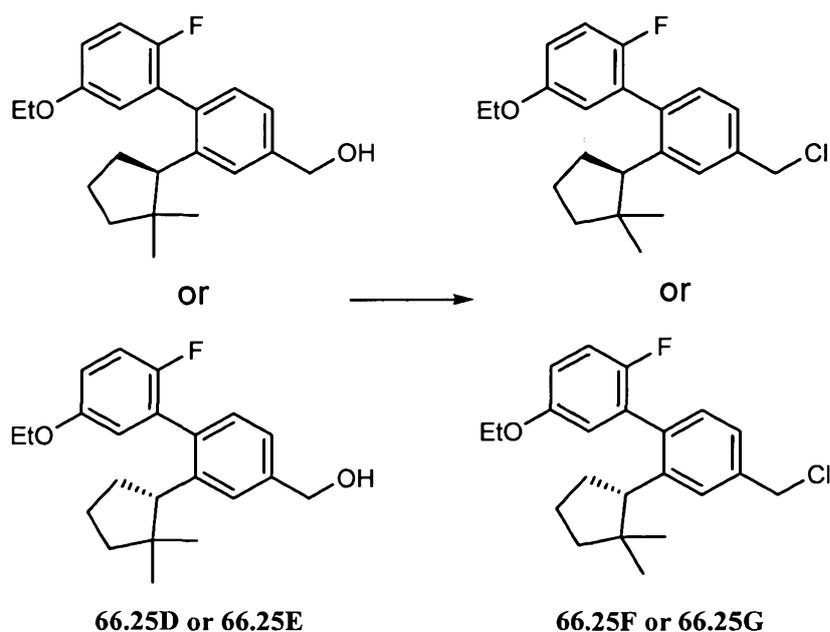
[0660] Methyl 2-(2,2-dimethylcyclopentyl)-5'-(ethoxy)-2'-fluoro-1,1'-biphenyl-4-carboxylate (66.25B). To a stirred solution of **66.25A** (0.400 g, 1.09 mmol) in MeOH (10.00 mL, 1.09 mmol) at 23°C was added palladium on carbon (0.116 g, 1.09 mmol). The reaction was placed under an atmosphere of hydrogen and stirred for 23 hours. The mixture was then filtered and concentrated in vacuo. The initial product was

then purified on silica gel (0-20% EtOAc in hexanes) to yield **66.25B** as a colorless oil (0.400 g, 99.5% yield).

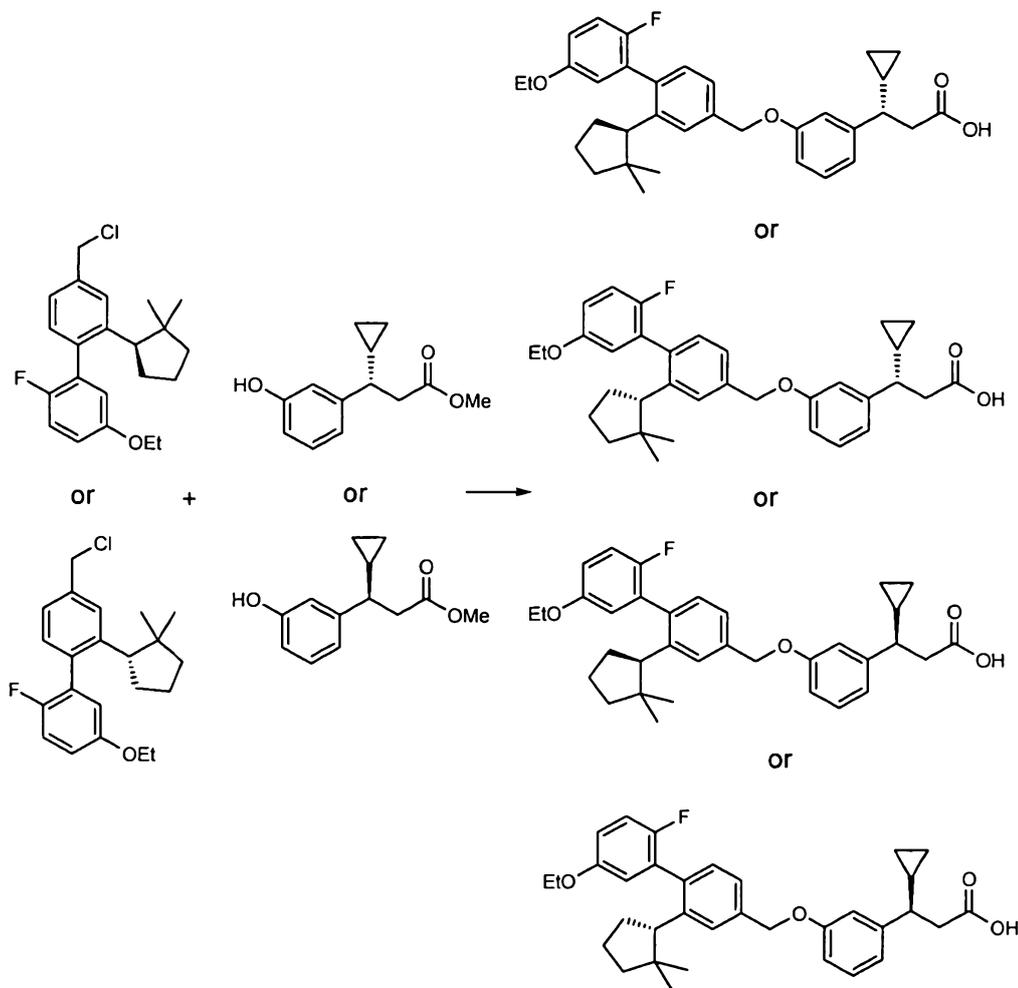


[0661] **(2-((1R)-2,2-Dimethylcyclopentyl)-5'-(ethoxy)-2'-fluoro-1,1'-biphenyl-4-yl)methanol and (2-((1S)-2,2-dimethylcyclopentyl)-5'-(ethoxy)-2'-fluoro-1,1'-biphenyl-4-yl)methanol (66.25D and 66.25E)**. To a stirred solution of **66.25B** (0.400 g, 1.1 mmol) in THF (15.00 mL, 183 mmol) at 0°C was added LAH in THF (2.2 mL, 2.2 mmol, 1.0M). The mixture was stirred for one hour and then 1N NaOH(aq) was added to quench the reaction. The reaction mixture was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the

organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **66.25C** as a colorless oil (0.320 g, 87% yield). Chiral separation of **66.25C** was accomplished on Chiracel-OD (3%IPA in hexane) to provide **66.25D** (peak one) and **66.25E** (peak two). Both enantiomers were used to synthesize example compounds, and both enantiomers gave active example compounds. However, the enantiomer corresponding to peak 2 provided the most active example compounds. ¹



[0662] 4-(Chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-5'-(ethoxy)-2'-fluoro-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-5'-(ethoxy)-2'-fluoro-1,1'-biphenyl (**66.25F** or **66.25G**). To a stirred solution of **66.25C** or **66.25D** (0.147 g, 0.43 mmol) in DCM (2.00 mL) at 23°C was added DMF (0.0033 mL) followed by thionyl chloride (0.063 mL, 0.86 mmol). The reaction was then stirred for 4 hours and then concentrated in vacuo. The initial product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.25F** or **66.25G** as a colorless oil (0.120 g, 77% yield).

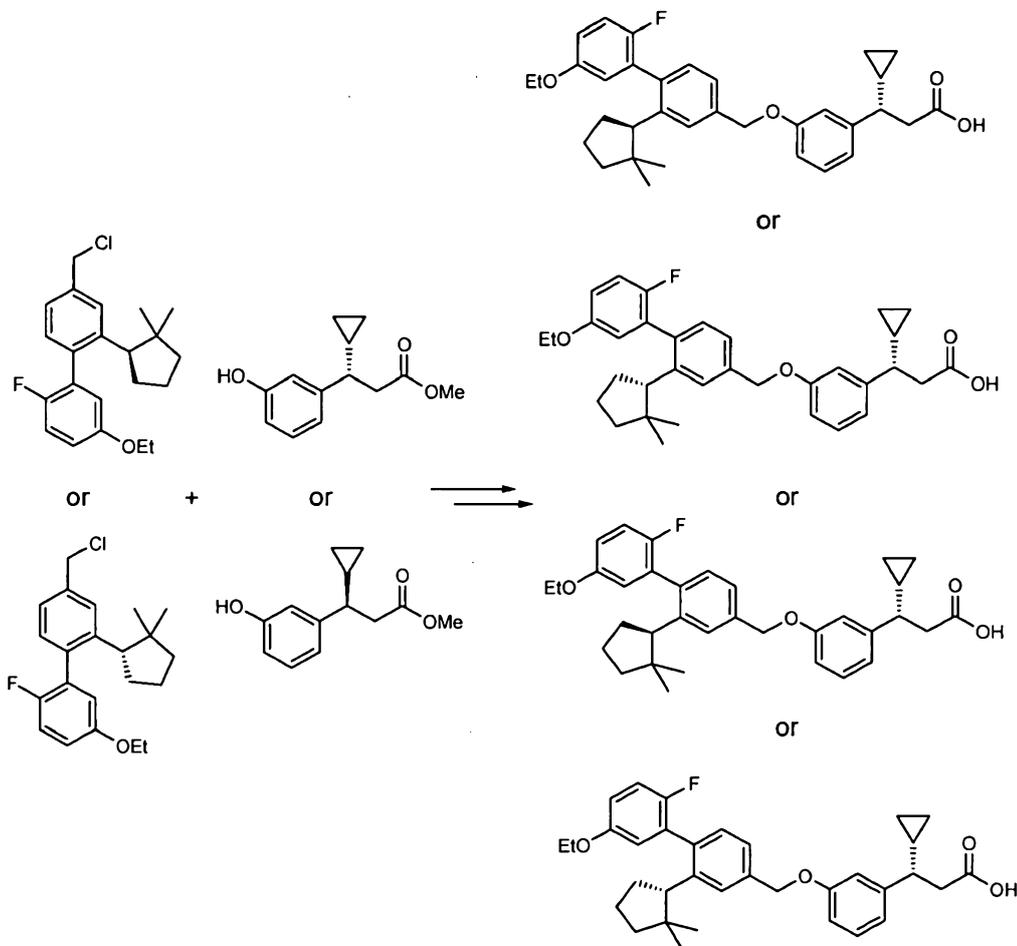


66.25F or 66.25G

66.6X

66.25

[0663] (3S)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-5'-(ethoxy)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-5'-(ethoxy)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-5'-(ethoxy)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-5'-(ethoxy)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.25). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using the chloromethyl compound derived from peak one from the chiral separation of 66.25C on the OD-column) to yield 66.25 (0.0337 g, 70% yield over two steps). MS ESI (neg.) m/e: 529.3 (M-H)⁺.

[0664] Example 66.26

66.25F or 66.25G

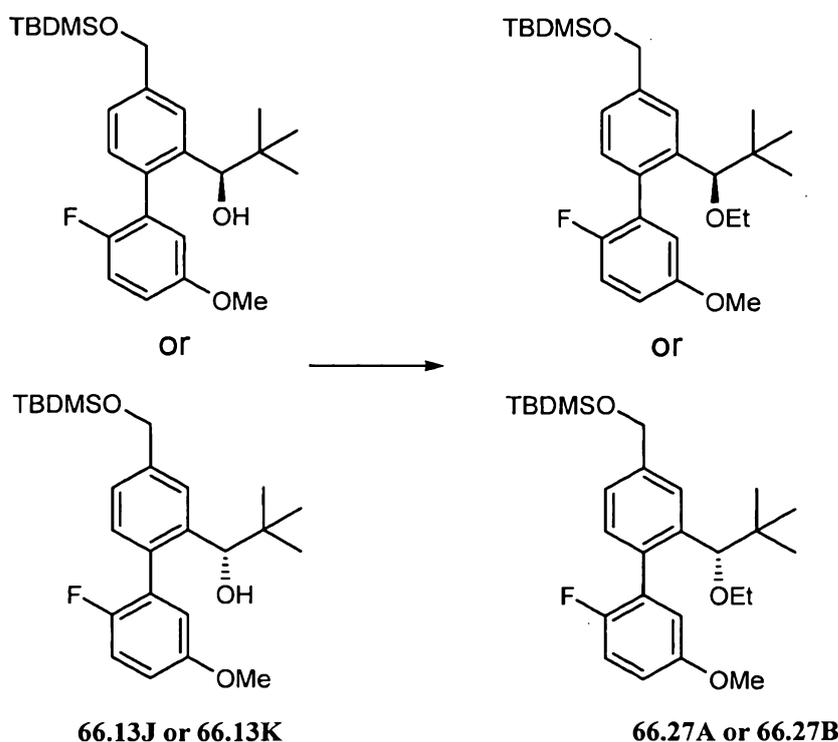
66.6X

66.26

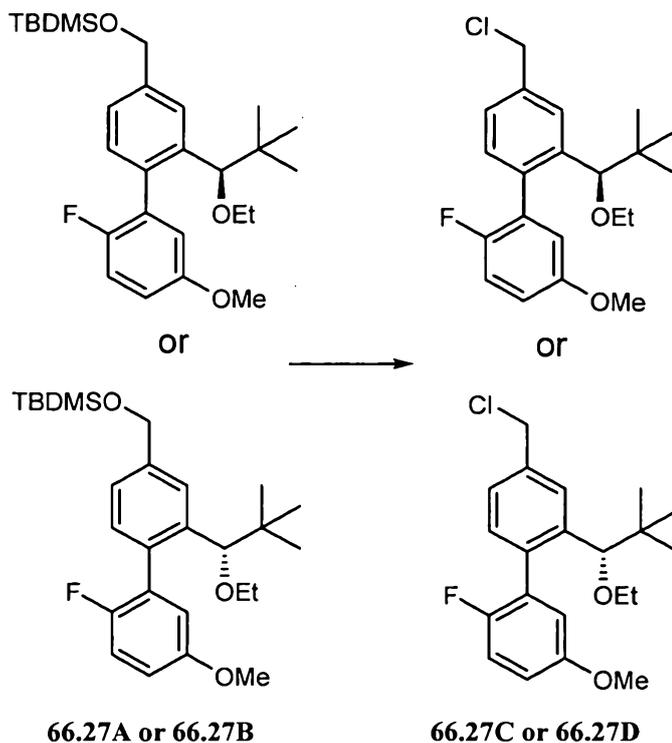
[0665] (3S)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-5'-(ethoxy)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-5'-(ethoxy)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-5'-(ethoxy)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-5'-(ethoxy)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.26). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using the chloromethyl compound derived from peak two from the chiral separation of 66.25C on the OD-column, described

herein) to yield **66.26** (0.0339 g, 71% yield over two steps). MS ESI (neg.) m/e: 529.3 (M-H)⁺.

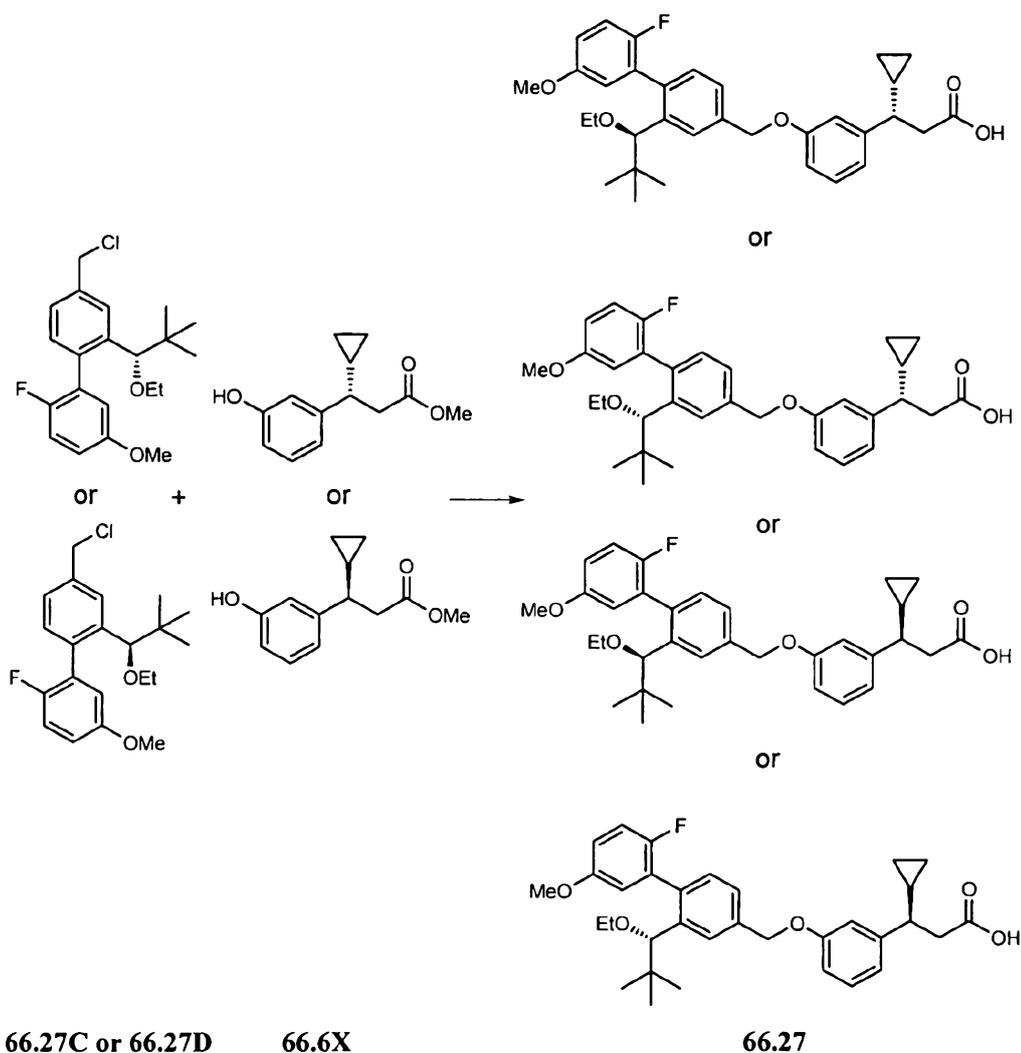
[0666]

Example 66.27

[0667] **(1,1-Dimethylethyl)((2-((1R)-1-(ethyloxy)-2,2-dimethylpropyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)dimethylsilane or (1,1-dimethylethyl)((2-((1S)-1-(ethyloxy)-2,2-dimethylpropyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)dimethylsilane (**66.27A or 66.27B**). To a stirred solution of **66.13J or 66.13K** (derived from peak two from chiral separation of **66.13G**) (0.110 g, 0.25 mmol) in DMF (2.00 mL) at 23°C was added iodoethane (0.048 g, 0.31 mmol), followed by sodium hydride (0.0073 g, 0.31 mmol). The mixture was stirred at 60°C for 21 hours and then cooled to room temperature. The reaction was diluted with brine and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.27A or 66.27B** as a colorless oil (0.065 g, 55% yield).**



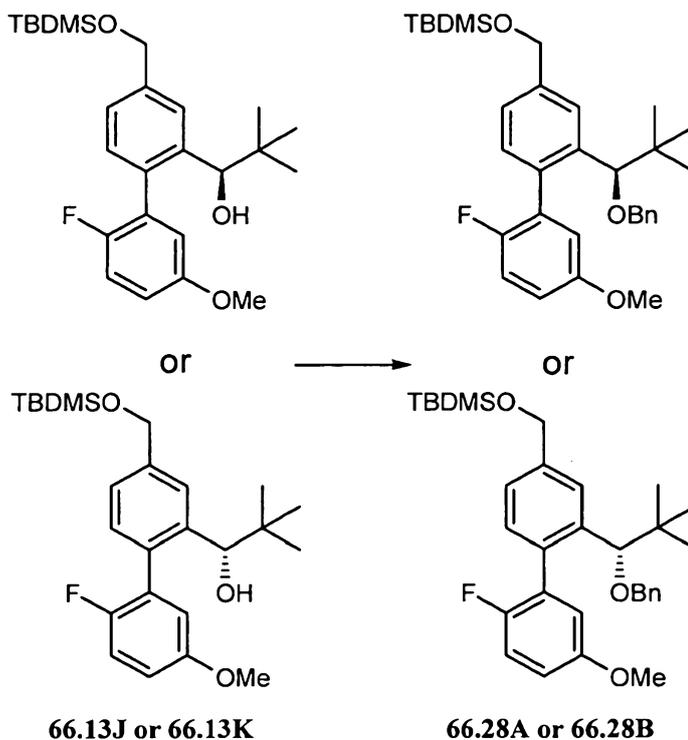
[0668] 4-(Chloromethyl)-2-((1R)-1-(ethoxy)-2,2-dimethylpropyl)-2'-fluoro-5-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-1-(ethoxy)-2,2-dimethylpropyl)-2'-fluoro-5-(methoxy)-1,1'-biphenyl **66.27C or 66.27D**). To a stirred solution of **66.27A or 66.27B** (0.065 g, 0.1 mmol) in DCM (2.00 mL) at 23°C was added DMF (0.001 mL) followed by thionyl chloride (0.02 mL, 0.3 mmol). The mixture was stirred for 2 hours and then concentrated in vacuo. The product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.27C or 66.27D** as a colorless oil (0.04 g, 78% yield).



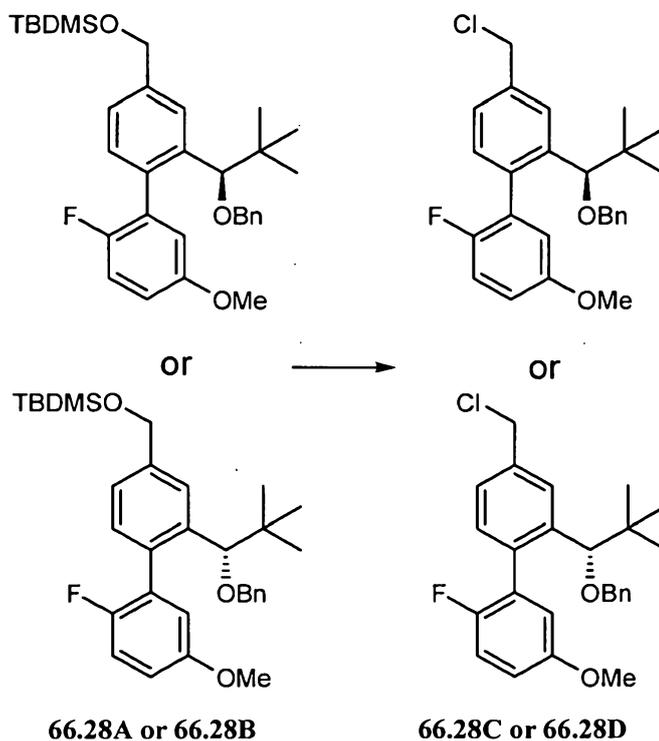
[0669] (3S)-3-Cyclopropyl-3-(3-(((2-((1R)-1-(ethyloxy)-2,2-dimethylpropyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-1-(ethyloxy)-2,2-dimethylpropyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-1-(ethyloxy)-2,2-dimethylpropyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-1-(ethyloxy)-2,2-dimethylpropyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.27). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 66.6X and the chloromethyl compound derived from peak two from the chiral separation

of **66.13G** from the OD-column) to yield **66.27** (0.0418 g, 69% yield over two steps).
MS ESI (neg.) m/e: 529.3 (M-H)⁺.

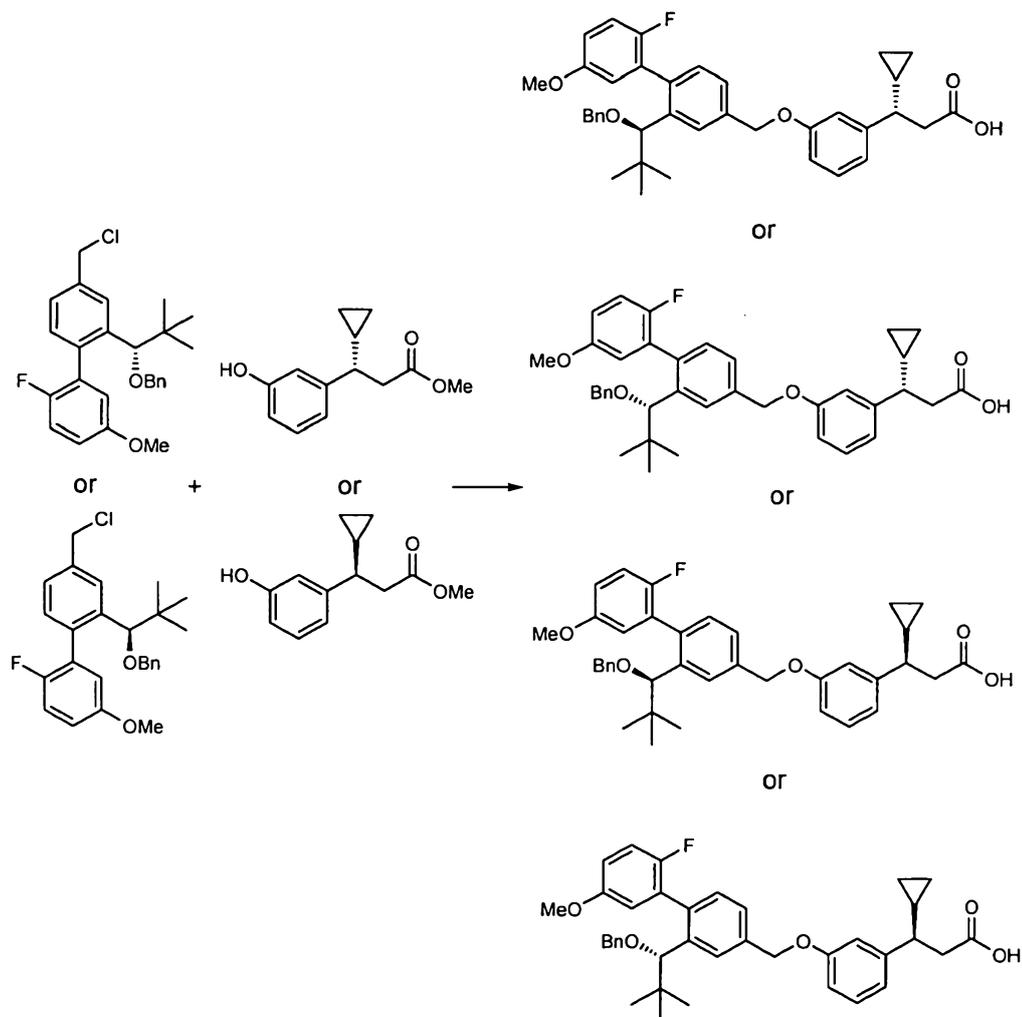
[0670] **Example 66.28**



[0671] **(1,1-Dimethylethyl)((2-((1R)-2,2-dimethyl-1-((phenylmethyl)oxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)dimethylsilane or (1,1-dimethylethyl)((2-((1S)-2,2-dimethyl-1-((phenylmethyl)oxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)dimethylsilane (**66.28A** or **66.28B**). To a stirred solution of **66.13J** or **66.13K** (derived from peak two from chiral separation of **66.13G**) (0.110 g, 0.25 mmol) in DMF (2.00 mL) at 23°C was added 1-(benzyloxy)methylbenzene (0.052 g, 0.31 mmol), followed by sodium hydride (0.0073 g, 0.31 mmol). The reaction was stirred at 60°C for 26 hours. The reaction was then cooled to room temperature, diluted with water, and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.28A** or **66.28B** as a colorless oil (0.132 g, 99% yield).**



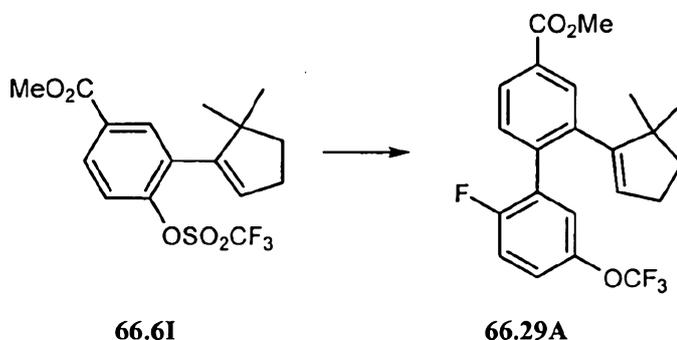
[0672] 4-(Chloromethyl)-2-((1R)-2,2-dimethyl-1-((phenylmethyl)oxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-2,2-dimethyl-1-((phenylmethyl)oxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (66.28C or 66.28D). To a stirred solution of **66.28A** or **66.28B** (0.132 g, 0.3 mmol) in DCM (2.00 mL) at 23°C was added DMF (0.002 mL) followed by thionyl chloride (0.04 mL, 0.5 mmol). The reaction was stirred for two hours and then the reaction was concentrated in vacuo. The initial product was purified on silica gel (0-10% EtOAc in hexanes) to yield **66.28C** or **66.28D** as a colorless oil (0.08 g, 74% yield).



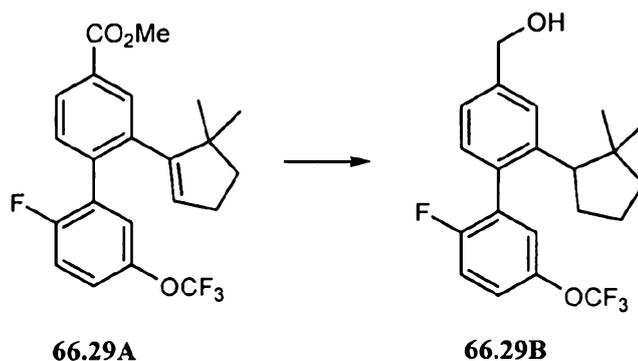
[0673] (3S)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-((phenylmethyl)oxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-((phenylmethyl)oxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-((phenylmethyl)oxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-((phenylmethyl)oxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.28). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 66.6X and the chloromethyl compound derived from peak two from chiral separation of 66.13G from the OD-column,

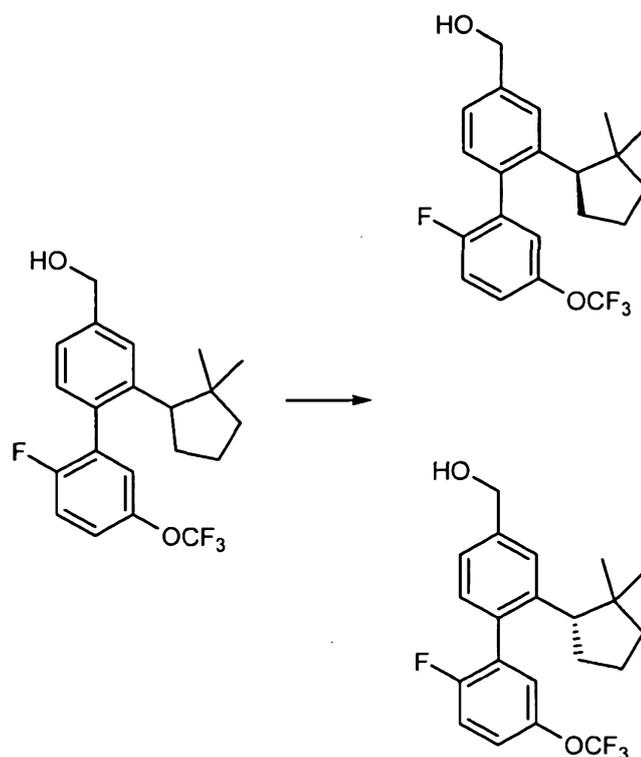
described herein) to yield **66.28** (0.0297 g, 44% yield over two steps). MS ESI (neg.) m/e: 595.3 (M-H)⁺.

[0674] **Example 66.29**



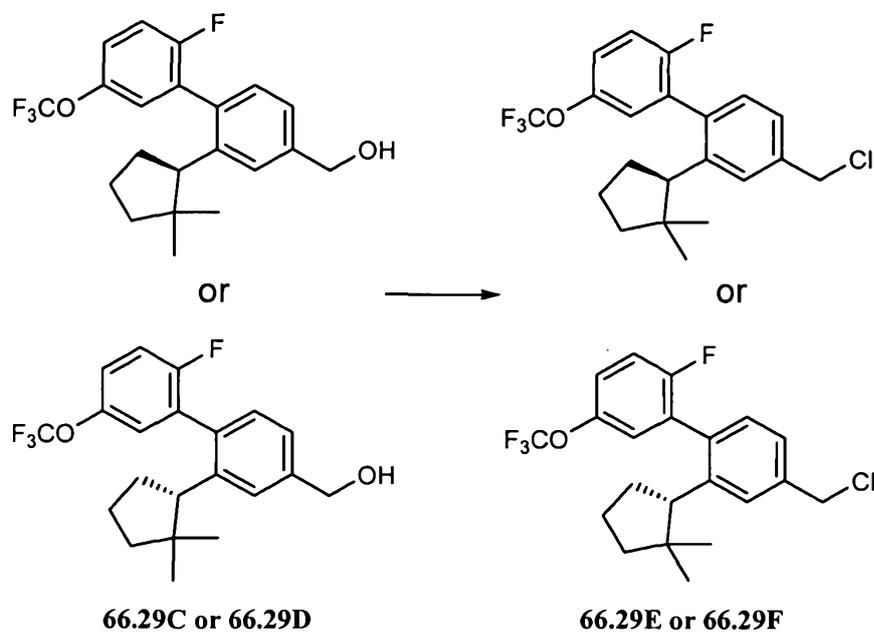
[0675] **Methyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-((trifluoromethyl)oxy)-1,1'-biphenyl-4-carboxylate 66.29A.** To a stirred solution of methyl 3-(5,5-dimethylcyclopent-1-en-1-yl)-4-(trifluoromethylsulfonyloxy)benzoate **66.6I** (0.400 g, 1.1 mmol) in DMF (4.00 mL) at 23°C was added 2-fluoro-5-(trifluoromethoxy)phenylboronic acid (0.36 g, 1.6 mmol, commercially available from Aldrich), potassium carbonate (0.44 g, 3.2 mmol), and then tetrakis(triphenylphosphine)palladium (0.12 g, 0.11 mmol). The mixture was heated to 90°C and stirred for 23 hours. The reaction was then cooled to room temperature, diluted with water, and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.29A** as a colorless oil (0.400 g, 93% yield).



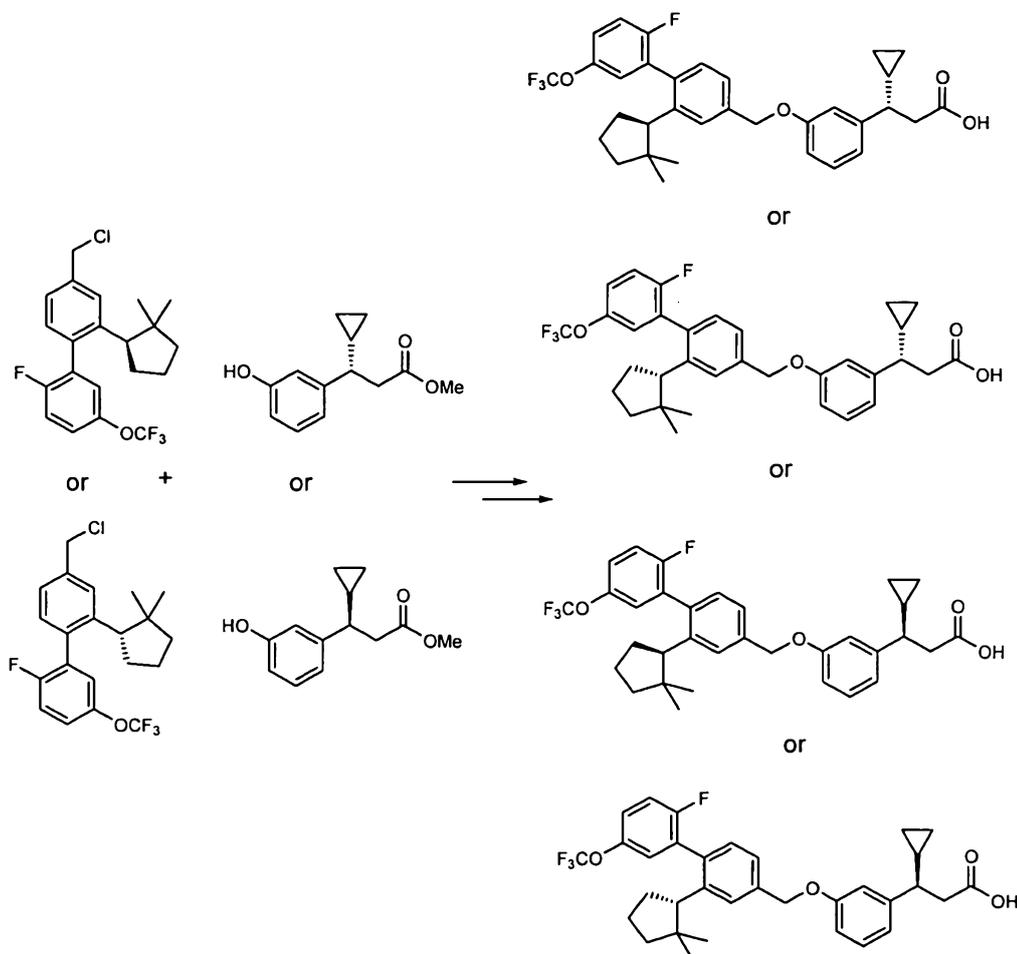
**66.29B****66.29C and 66.29D**

[0676] **(2-((1R)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-((trifluoromethyl)oxy)-1,1'-biphenyl-4-yl)methanol and (2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-((trifluoromethyl)oxy)-1,1'-biphenyl-4-yl)methanol (66.29C and 66.29D).** To a stirred solution of **66.29A** (0.325 g, 1.09 mmol) in MeOH (10.00 mL) at 23°C was added palladium on carbon (0.116 g, 1.09 mmol). The reaction was placed under an atmosphere of hydrogen and stirred for 23 hours. The reaction mixture was then filtered and concentrated in vacuo. The product thus obtained was used without further purification. To a stirred solution of the product (0.325 g, 0.79 mmol) in THF (15.00 mL, 183 mmol) at 0°C was added LAH in THF (1.6 mL, 1.6 mmol, 1.0M) and the mixture was stirred for two hours. 1N NaOH(aq) was added to quench the reaction, and the quenched mixture was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **66.29B** as a colorless oil (0.270 g, 89% yield). Chiral separation of **66.29B** was accomplished on Chiracel-OD (3%IPA in hexane) to provide **66.29C** and **66.29D**. Both enantiomers were used to synthesize example compounds, and both

enantiomers gave active example compounds. However, the enantiomer corresponding to peak 2 provided the most active example compounds.¹



[0677] 4-(Chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(trifluoromethyl)oxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(trifluoromethyl)oxy)-1,1'-biphenyl (**66.29E** or **66.29F**). To a stirred solution of **66.29C** or **66.29D** (0.086 g, 0.22 mmol) in DCM (2.00 mL) at 23°C was added DMF (0.0017 mL) followed by thionyl chloride (0.033 mL, 0.45 mmol). The reaction was stirred for 2 hours and then concentrated in vacuo. The product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.29E** or **66.29F** as a colorless oil (0.085 g, 94% yield).



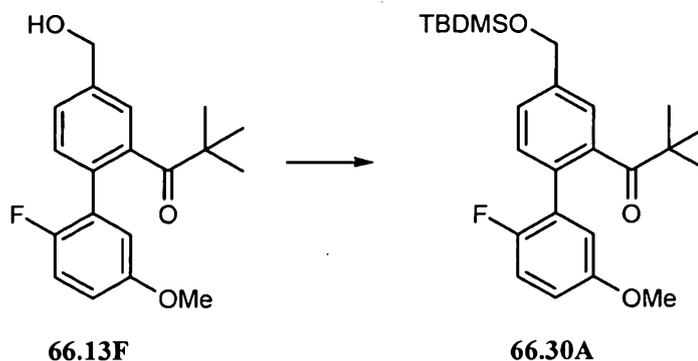
66.29E or 66.29F

66.6X

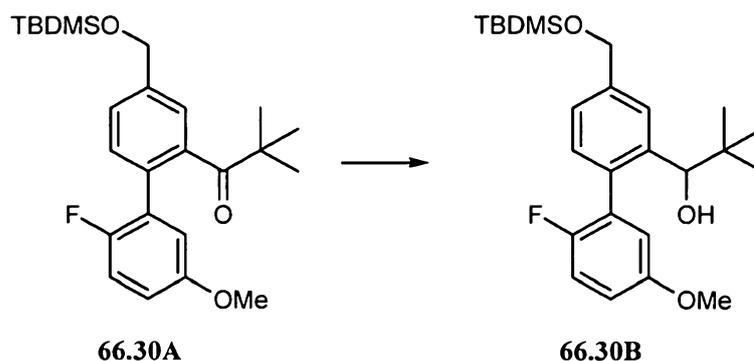
66.29

[0678] (3S)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-((trifluoromethyl)oxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-((trifluoromethyl)oxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-((trifluoromethyl)oxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-((trifluoromethyl)oxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.29).

The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 66.6X and the chloromethyl compound derived from peak two from the chiral separation of 66.29B from the OD-column, described herein) to yield 66.29 (0.0483 g, 75% yield over two steps). MS ESI (neg.) m/e: 569.2 (M-H)⁺.

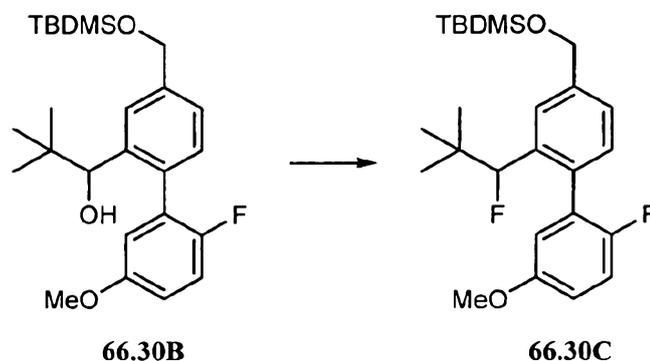
[0679] Example 66.30

[0680] 1-(4-(((1,1-Dimethylethyl)(dimethyl)silyl)oxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanone (**66.30A**). To a stirred solution of **66.13F** (1.00 g, 3 mmol) in DCM (10.00 mL) at 23°C was added tert-butyldimethylsilyl chloride (0.6 mL, 4 mmol), followed by TEA (0.5 mL, 4 mmol) and DMAP (0.04 g, 0.3 mmol). The reaction was stirred for 16 hours and then the reaction was concentrated in vacuo. The product was purified on silica gel (0-10% EtOAc in hexanes) to yield **66.30A** as a colorless oil (1.30 g, 96% yield).

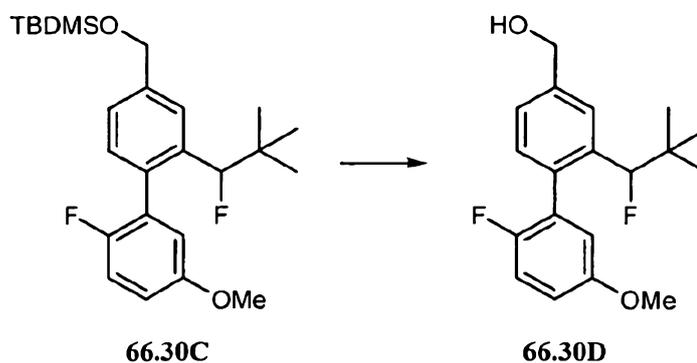


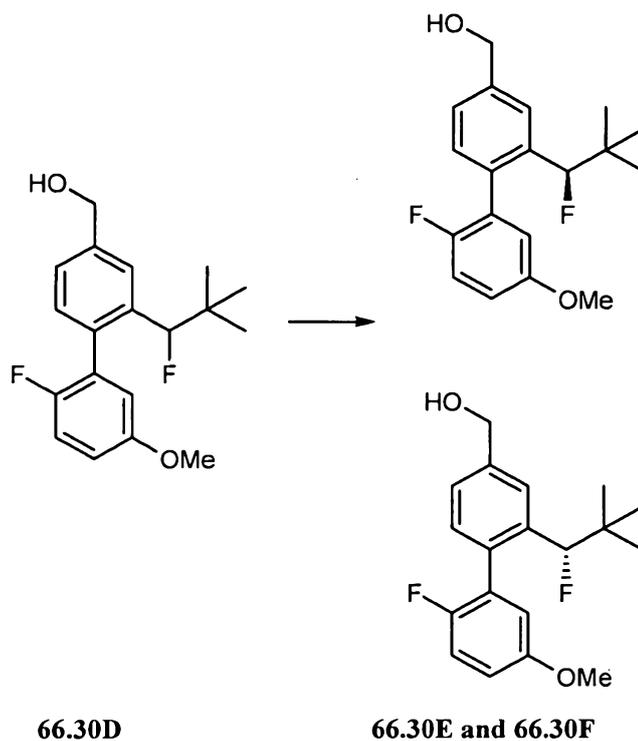
[0681] 1-(4-(((1,1-Dimethylethyl)(dimethyl)silyl)oxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol (**66.30B**). To a stirred solution of **66.30A** (0.500 g, 1.2 mmol) in THF (15.00 mL, 183 mmol) at 0°C was added LAH in THF (2.3 mL, 2.3 mmol, 1.0M). The reaction was stirred for two hours. 1N NaOH(aq) was added to quench the reaction mixture, and the reaction was then extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then

purified on silica gel (0-10% EtOAc in hexanes) to yield **66.30B** as a colorless oil (0.400 g, 80% yield).

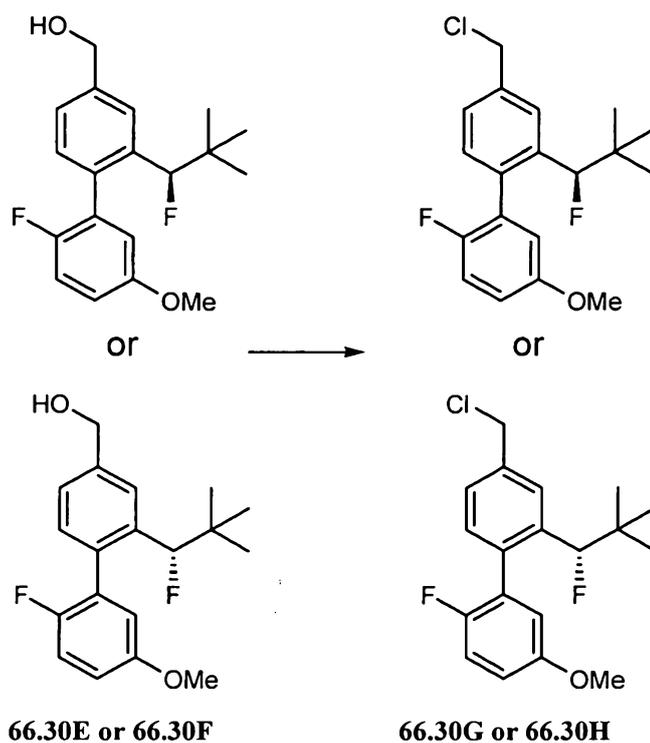


[0682] **(1,1-Dimethylethyl)((2'-fluoro-2-(1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxydimethylsilane (66.30C)**. To a solution of **66.30B** (0.400 g, 0.925 mmol) in toluene (10 mL) at -78°C was added DAST (0.209 g, 1.29 mmol) dropwise. The reaction was stirred at -78°C for 30 minutes and then warmed to 23°C and stirred for an additional 2 hours. Water was added to quench the reaction mixture. The reaction was then extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.30C** as a colorless oil (0.400 g, 99% yield).

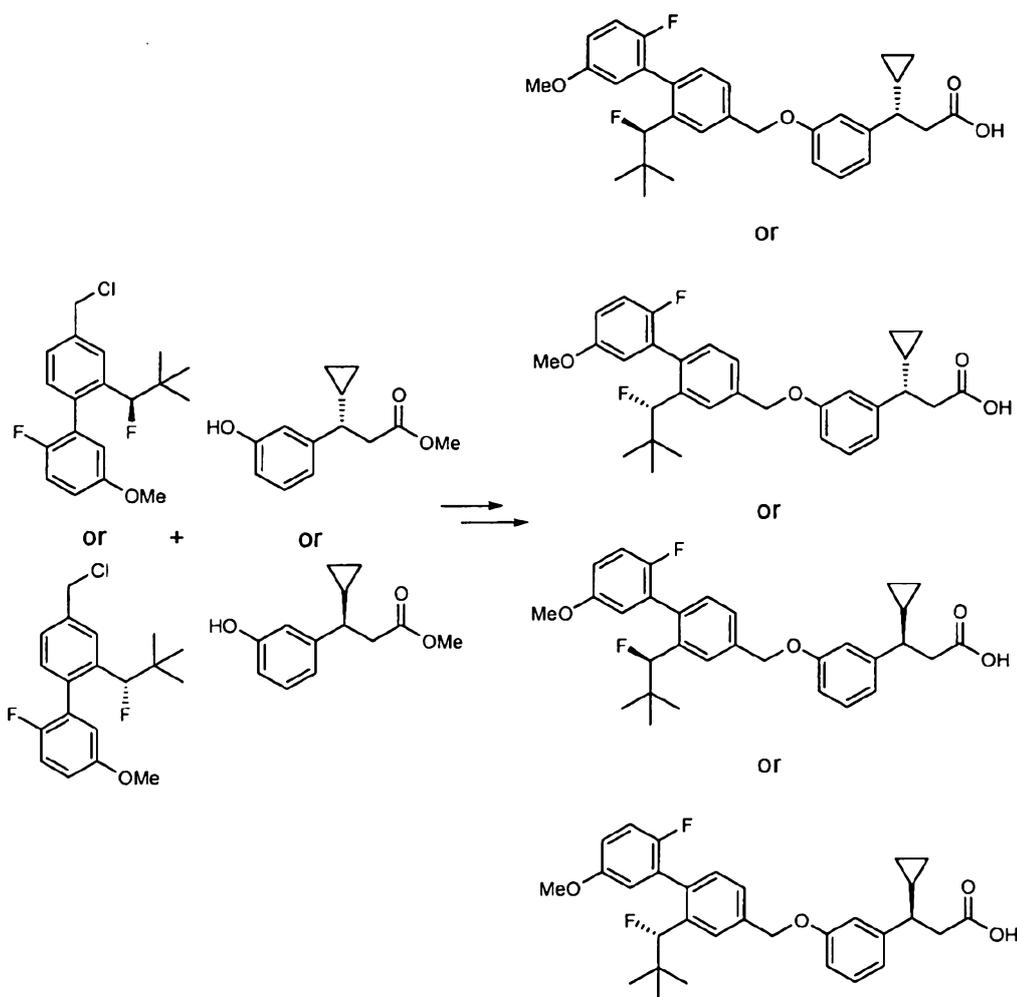




[0683] (2'-Fluoro-2-((1R)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol and (2'-fluoro-2-((1S)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (**66.30E** and **66.30F**). To a stirred solution of **66.30C** (0.400 g, 0.920 mmol) in MeOH (10.00 mL) at 23°C was added PPTS (0.0231 g, 0.0920 mmol). The reaction was stirred for 19 hours and then concentrated in vacuo to give a clear oil. The product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **66.30D** as a colorless oil (0.272 g, 92% yield). Chiral separation of **66.30D** was accomplished on Chiracel-OD (3%IPA in hexane) to provide **66.30E** and **66.30F**. Both enantiomers were used to synthesize example compounds, and both enantiomers gave active example compounds. However, the enantiomer corresponding to peak 2 provided the most active example compounds.



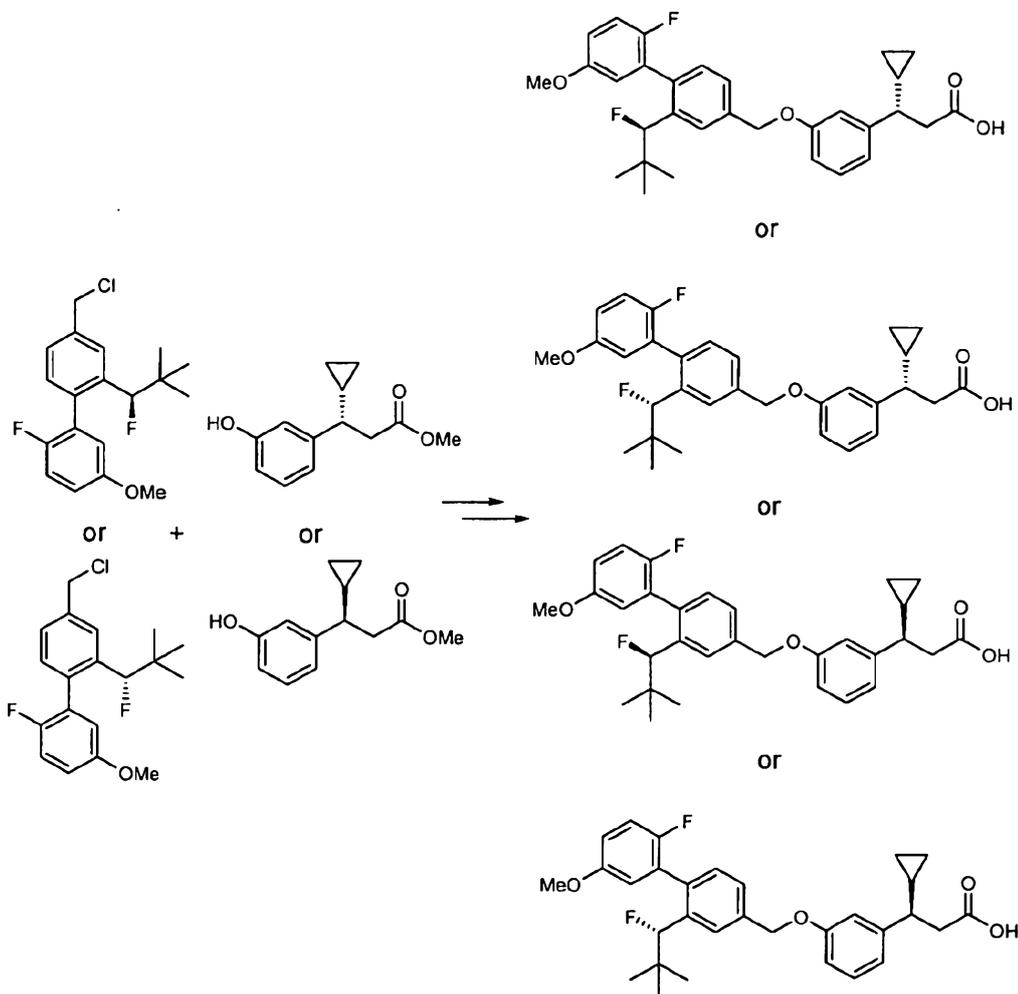
[0684] **4-(Chloromethyl)-2'-fluoro-2-((1R)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2'-fluoro-2-((1R)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl (66.30G or 66.30H).** To a stirred solution of **66.30E** or **66.30F** (0.102 g, 0.3 mmol) in DCM (2.00 mL) at 23°C was added DMF (0.002 mL) followed by thionyl chloride (0.05 mL, 0.6 mmol). The reaction was stirred for 1.5 hours. The reaction was concentrated in vacuo. The product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.30G** or **66.30H** as a colorless oil (0.09 g, 83% yield).



[0685] (3S)-3-Cyclopropyl-3-(3-(((2'-fluoro-2-((1R)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2'-fluoro-2-((1S)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2'-fluoro-2-((1R)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2'-fluoro-2-((1S)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.30). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 66.6X and the chloromethyl compound derived from peak one from chiral separation of 66.30D from the OD-column,

described herein) to yield **66.30** (0.0467 g, 80% yield over two steps). MS ESI (neg.) m/e: 507.2 (M-H)⁺.

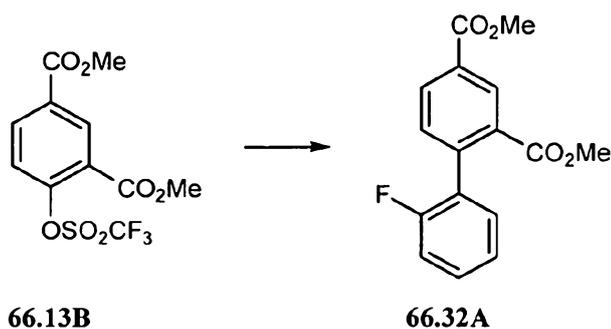
[0686] **Example 66.31**



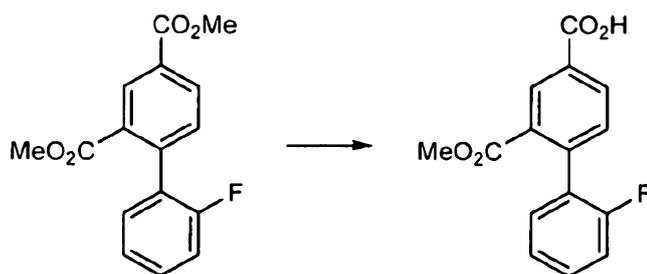
[0687] (3S)-3-Cyclopropyl-3-(3-(((2'-fluoro-2-((1R)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2'-fluoro-2-((1S)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2'-fluoro-2-((1R)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2'-fluoro-2-((1S)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-

yl)methyloxy)phenyl)propanoic acid (**66.31**). The alkylation and hydrolysis were conducted in an analogous manner to Example **66.6** (using **66.6X** and the chloromethyl compound derived from peak two from the chiral separation of **66.30D** from the OD-column, described herein) to yield **66.31** (0.059 g, 85% yield over two steps). MS ESI (neg.) m/e: 507.2 (M-H)⁺.

[0688] **Example 66.32**



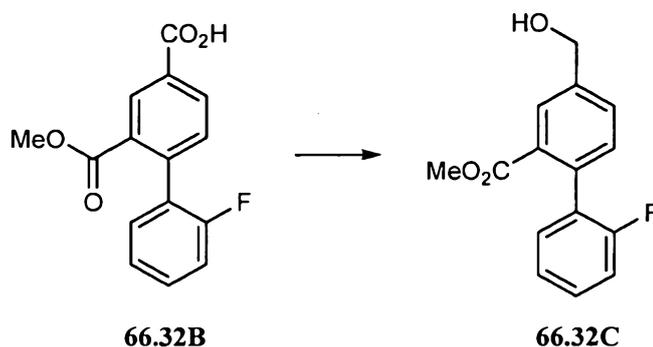
[0689] **Dimethyl 2'-fluoro-1,1'-biphenyl-2,4-dicarboxylate (66.32A)**. To a stirred solution of dimethyl 4-(trifluoromethylsulfonyloxy)isophthalate **66.13B** (1.60 g, 4.7 mmol) in DMF (9.4 mL, 4.7 mmol) at 23°C was added 2-fluorophenylboronic acid (0.98 g, 7.0 mmol, commercially available from Aldrich), potassium carbonate (1.9 g, 14 mmol), and then tetrakis(triphenylphosphine)palladium (0.54 g, 0.47 mmol). The reaction mixture was heated to 90°C and the reaction was stirred for 22 hours. The reaction was then cooled to room temperature, diluted with water, and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.32A** as a colorless oil (1.10 g, 82% yield).



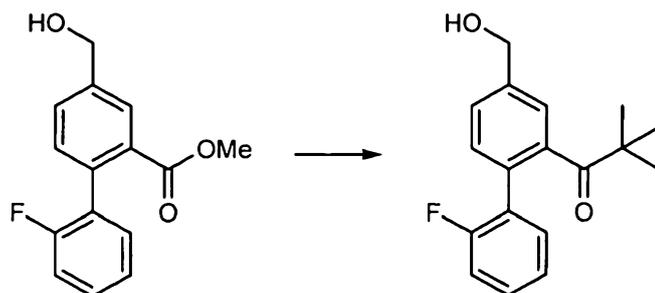
66.32A

66.32B

[0690] **2'-Fluoro-2-((methoxy)carbonyl)-1,1'-biphenyl-4-carboxylic acid (66.32B).** To a stirred solution of **66.32A** (1.00 g, 3.5 mmol) in THF (70.0 mL) and MeOH (70.0 mL) at 0°C was slowly added potassium hydroxide (1.9 mL, 3.8 mmol) to maintain the temperature below 6°C. The reaction mixture was allowed to warm to room temperature and stirred for 48 hours. The reaction mixture was then concentrated in vacuo, acidified with 1N HCl, and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and to give a white solid **66.32B** (0.90 g, 95% yield).

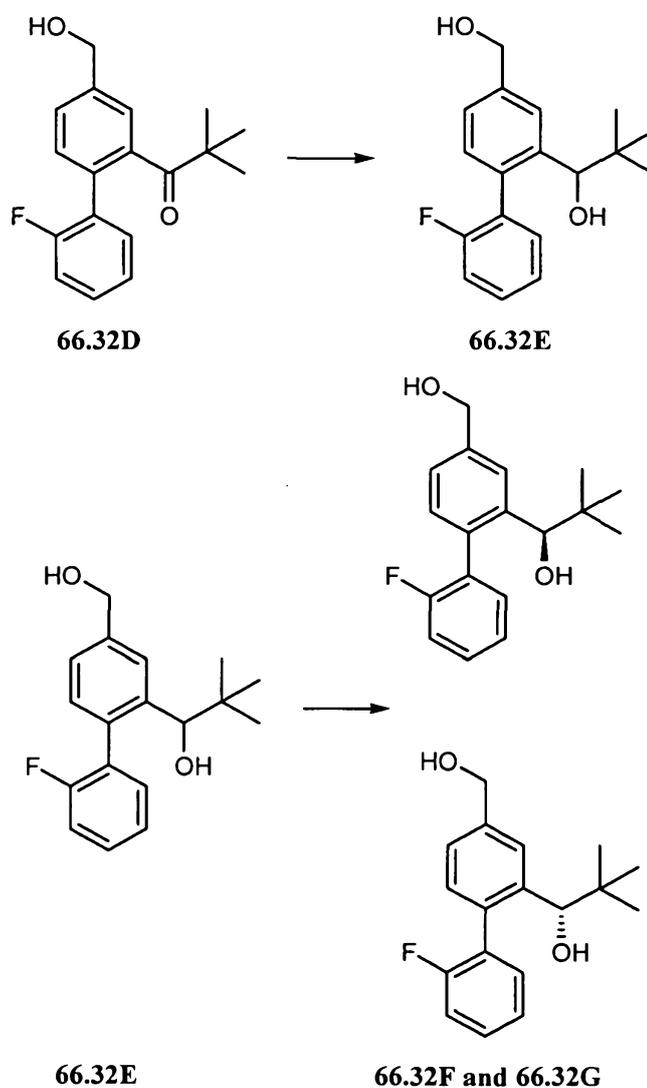


[0691] **Methyl 2'-fluoro-4-(hydroxymethyl)-1,1'-biphenyl-2-carboxylate (66.32C).** To a stirred solution of **66.32B** (0.90 g, 3 mmol) in THF (33 mL) at 0°C was added borane-THF complex (7 mL, 7 mmol, 1.0M). The reaction was allowed to warm to 23°C and stirred for 7 hours. The reaction mixture was then concentrated in vacuo. The reaction was diluted with 1N HCl and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-40% EtOAc in hexanes) to yield **66.32C** as a colorless solid (0.850 g, 100% yield).

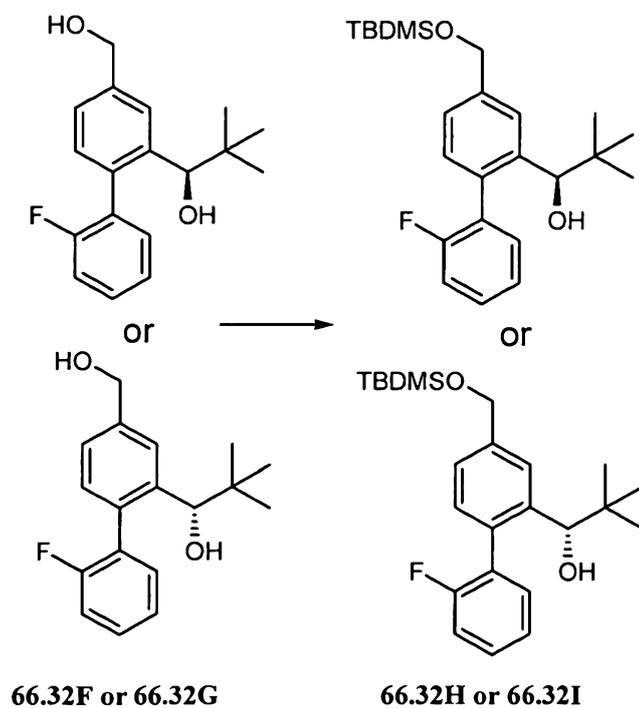


66.32C**66.32D**

[0692] **1-(2'-Fluoro-4-(hydroxymethyl)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanone (66.32D)**. To a stirred solution of **66.32C** (0.850 g, 3 mmol) in THF (33 mL) at -78°C was added tert-butyllithium (6 mL, 10 mmol, 1.7M). The reaction was stirred for 5 hours and then a saturated solution of ammonium chloride was added and the mixture was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-40% EtOAc in hexanes) to yield **66.32D** as a colorless oil (0.670 g, 72% yield).

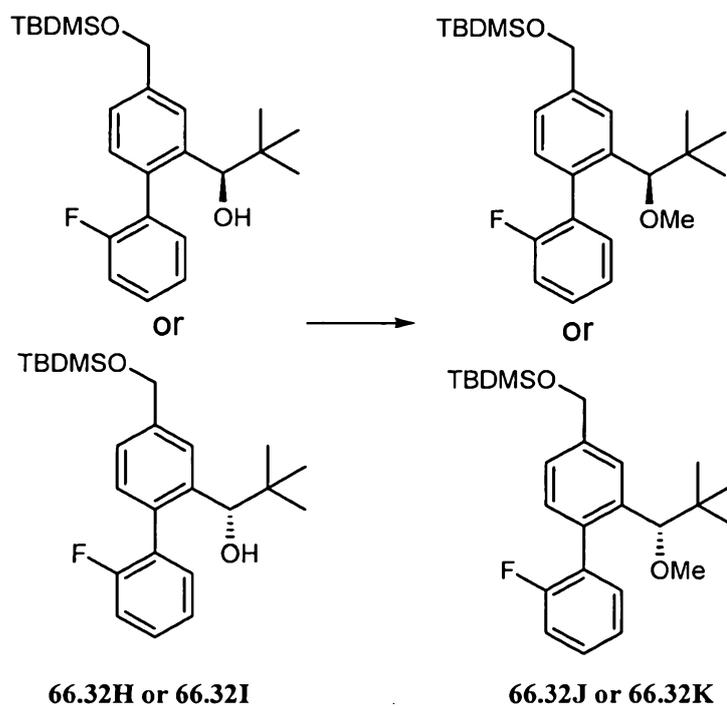


[0693] (1R)-1-(2'-Fluoro-4-(hydroxymethyl)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol and (1S)-1-(2'-fluoro-4-(hydroxymethyl)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol (**66.32 F** and **66.32G**). To a stirred solution of **66.32D** (0.670 g, 2 mmol) in THF (6 mL) at 0°C was added LAH in THF (5 mL, 5 mmol, 1.0M). The reaction was stirred for 1.5 hours and then 1N NaOH(aq) was added to quench the reaction mixture. The reaction was then extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was purified on silica gel (0-20% EtOAc in hexanes) to yield **66.32E** as a colorless oil (0.450 g, 67% yield). Chiral separation of **66.32E** was accomplished on Chiracel-OD (3%IPA in hexane) to provide **66.32F** and **66.32G**. Both enantiomers were used to synthesize example compounds, and both enantiomers gave active example compounds. However, the enantiomer corresponding to peak 2 provided the most active example compounds.

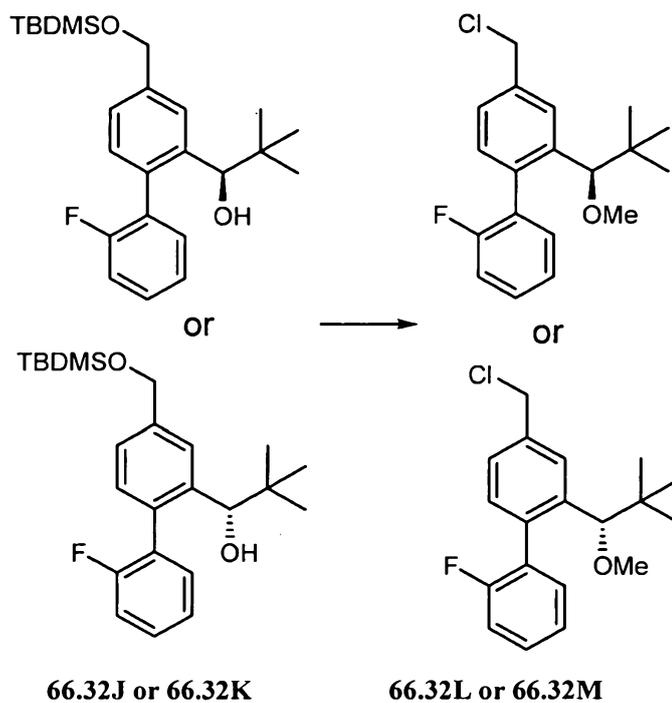


[0694] (1R)-1-(4-(((1,1-Dimethylethyl)(dimethyl)silyl)oxy)methyl)-2'-fluoro-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol or (1S)-1-(4-(((1,1-dimethylethyl)(dimethyl)silyl)oxy)methyl)-2'-fluoro-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol (**66.32H** or **66.32I**). To a stirred solution of **66.32F** or **66.32G** (0.200 g, 0.7 mmol) in DCM (10.00 mL) at 23°C was added tert-butyldimethylsilyl chloride (0.1 mL,

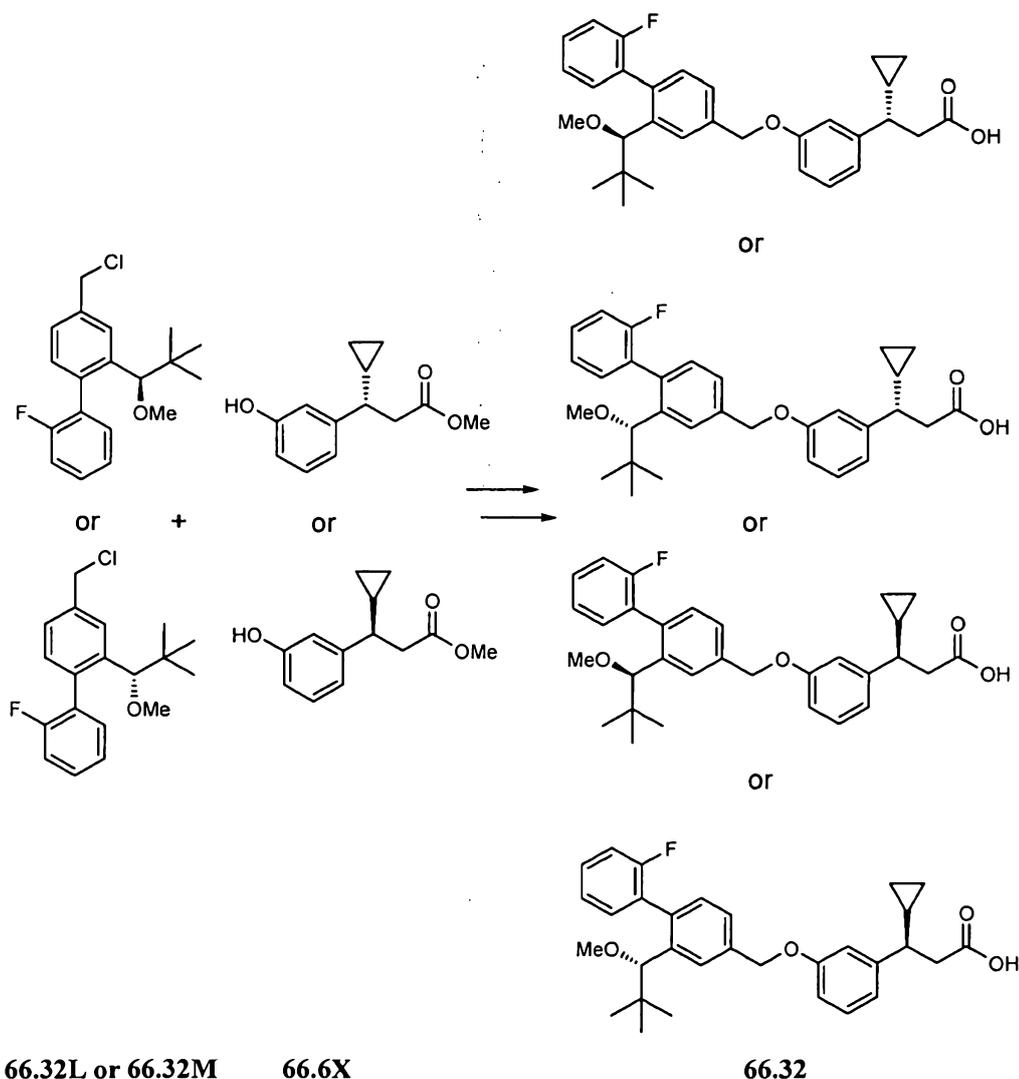
0.8 mmol), followed by TEA (0.1 mL, 0.8 mmol) and DMAP (0.008 g, 0.07 mmol). The reaction was stirred for 14 hours and then concentrated in vacuo. The product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **66.32H** or **66.32I** as a colorless oil (0.250 g, 90% yield).



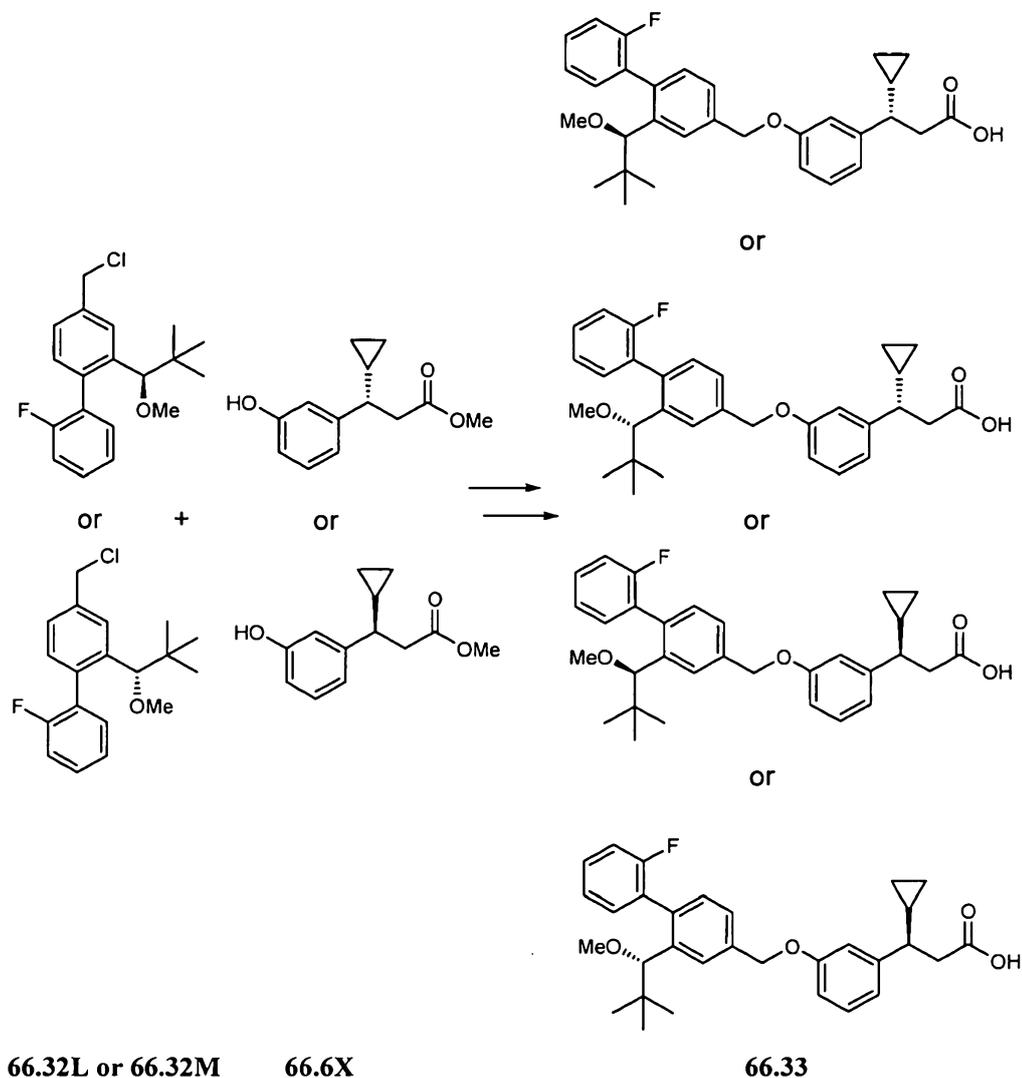
[0695] **(1,1-Dimethylethyl)((2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)dimethylsilane** or **(1,1-dimethylethyl)((2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)dimethylsilane** (**66.32J** **66.32K**). To a stirred solution of **66.32H** or **66.32I** (0.060 g, 0.15 mmol) in DMF (2.00 mL) at 23°C was added iodomethane (0.025 g, 0.18 mmol), followed by sodium hydride (0.0043 g, 0.18 mmol). The reaction was stirred at 60 °C for 19 hours, diluted with water, and the mixture was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-5% EtOAc in hexanes) to yield **66.32J** or **66.32K** as a colorless oil (0.062 g, 100% yield).



[0696] **4-(Chloromethyl)-2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-1,1'-biphenyl (66.32L 66.32M).** To a stirred solution of **66.32J** or **66.32K** (0.071 g, 0.17 mmol) in DCM (1.7 mL) and DMF (0.013 mL) at 0°C was added thionyl chloride (0.025 mL, 0.34 mmol). The reaction was stirred at room temperature for 1.5 hours and then concentrated in vacuo. The product was then purified on silica gel (0-5% EtOAc in hexanes) to yield **66.32L** or **66.32M** as a colorless oil (0.036 g, 66% yield).



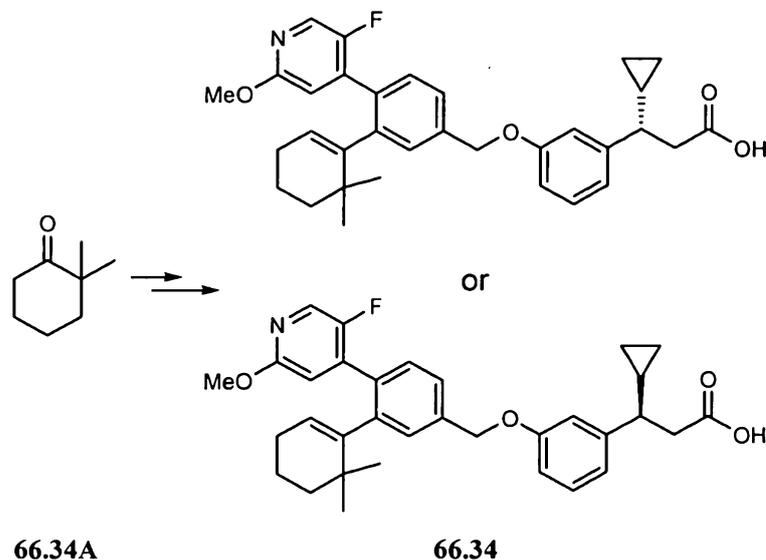
[0697] (3S)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid **66.32**. The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using **66.6X** and the chloromethyl compound derived from peak one from chiral separation of **66.32E** from the OD-column) to yield **66.32** (0.024 g, 43% yield over two steps). MS ESI (neg.) m/e: 489.2 (M-H)⁺.

[0698] Example 66.33

[0699] (3S)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.33). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 66.6X and the chloromethyl

compound derived from peak two from chiral separation of **66.32E** from the OD-column, described herein) to yield **66.33** (0.026 g, 48% yield over two steps). MS ESI (neg.) m/e: 489.2 (M-H)⁺.

[0700] **Example 66.34**



[0701] **(3S)-3-Cyclopropyl-3-(3-(((3-(6,6-dimethyl-1-cyclohexen-1-yl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)phenyl)propanoic acid or (3S)-3-Cyclopropyl-3-(3-(((3-(6,6-dimethyl-1-cyclohexen-1-yl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)phenyl)propanoic acid (66.34)**. This compound was prepared using a method analogous to that described for **66.12** starting from 2,2-dimethylcyclohexanone **66.34A** which is commercially available from Carbocore. MS ESI (neg.) m/e: 528.3 (M-H)⁺.

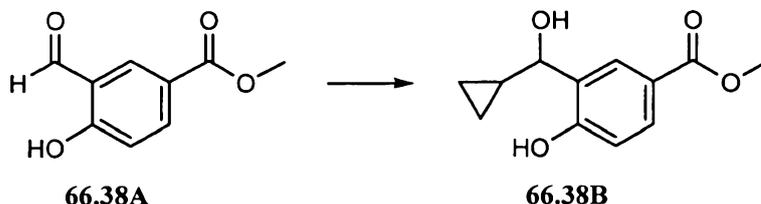
[0702] **(3S)-3-Cyclopropyl-3-(3-(((3-(6,6-dimethyl-1-cyclohexen-1-yl)-4-(5-fluoro-2-oxo-1,2-dihydro-4-pyridinyl)phenyl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((3-(6,6-dimethyl-1-cyclohexen-1-yl)-4-(5-fluoro-2-oxo-1,2-dihydro-4-pyridinyl)phenyl)methyl)oxy)phenyl)propanoic acid (66.35)**. To a reaction vessel containing **66.34** (26 mg, 0.049 mmol) was added 1.1 mL dioxane and 0.2 mL concentrated HCl. The reaction was heated at 60°C for 16 hours, neutralized with NaHCO₃, and extracted with EtOAc. Purification by silica gel column chromatography with MeOH/DCM afforded 10 mg of **66.35**. MS ESI (pos.) m/e: 516.3 (M+H)⁺.

[0703] **(3S)-3-Cyclopropyl-3-(3-(((3-((1S)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)phenyl)propanoic acid or (3S)-**

3-cyclopropyl-3-(3-(((3-((1R)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methoxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((3-((1S)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methoxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((3-((1R)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methoxy)phenyl)propanoic acid (66.36). The title compound was prepared in similar method as 66.6 through the hydrogenation of intermediate 66.12C. The detailed synthesis of the chloromethyl half is described in 83.4C. MS ESI (neg.) m/e: 516.3 (M-H)⁺.

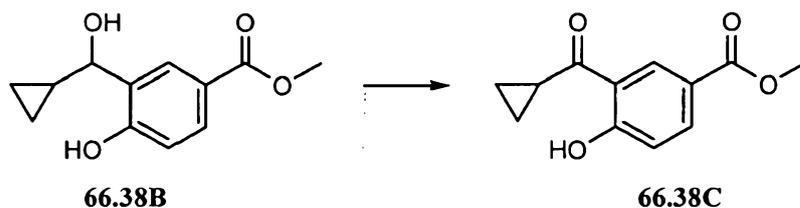
[0704] (3S)-3-Cyclopropyl-3-(3-(((3-((1R)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methoxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((3-((1S)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methoxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((3-((1R)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methoxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((3-((1S)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methoxy)phenyl)propanoic acid (66.37). This compound was prepared in similar method as 66.6 through the hydrogenation of intermediate 66.12C. The detailed synthesis of the chloromethyl half is described in 83.5. MS ESI (neg.) m/e: 516.3 (M-H)⁺.

[0705] Example 66.38

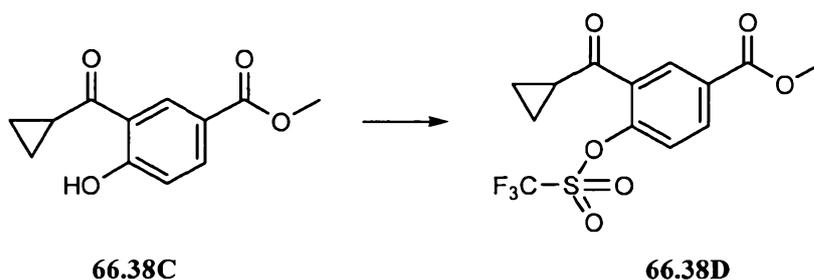


[0706] Methyl 3-(cyclopropyl(hydroxy)methyl)-4-hydroxybenzoate (66.38B).

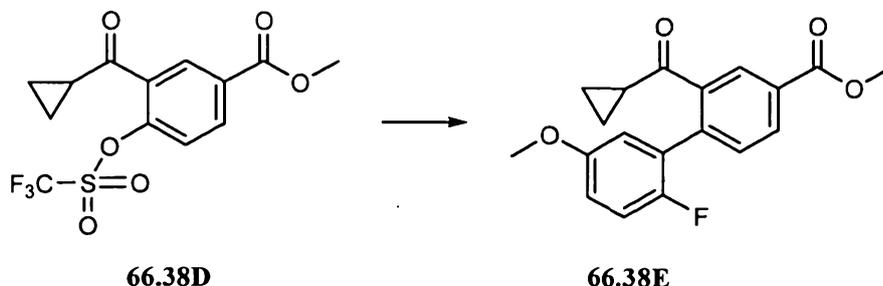
In an ice-bath, methyl 3-formyl-4-hydroxybenzoate **66.38A** (900 mg, 5 mmol) (commercially available from Aldrich) was dissolved in 5 mL THF. Then cyclopropylmagnesium bromide, 0.5 M in THF (22000 μ L, 11 mmol) (commercially available from Aldrich) was added slowly. The reaction was raised to room temperature immediately and stirred at room temperature for 2 hours. After quenching with 1N HCl 11 mL, the reaction was extracted with EtOAc and dried. Silica gel chromatography afforded 950 mg of the product **66.38B** (85%).



[0707] Methyl 3-(cyclopropanecarbonyl)-4-hydroxybenzoate (66.38C). To a flask with methyl 3-(cyclopropyl(hydroxy)methyl)-4-hydroxybenzoate (**66.38B**) (845 mg, 0.38 mmol) was added manganese (IV) oxide (1.65 g, 1.9 mmol). Then dioxane 3.5 mL was added and the reaction was heated at reflux for 4 hours. The reaction was filtered and concentrated and silica gel chromatography afforded 693 mg of **66.38C** (83%).

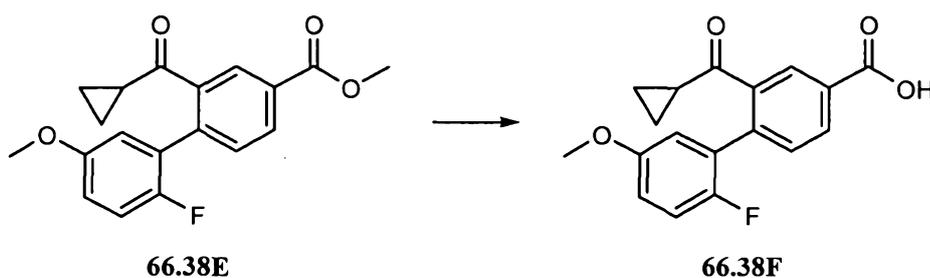


[0708] Methyl 3-(cyclopropanecarbonyl)-4-(trifluoromethylsulfonyloxy)benzoate (66.38D). To a flask with methyl 3-(cyclopropanecarbonyl)-4-hydroxybenzoate **66.38C** (693 mg, 3.1 mmol) was added DMAP (38mg, 0.31 mmol), and the mixture was flushed with nitrogen. DCM was then added followed by TEA (0.88 mL, 6.3 mmol). After stirring at room temperature for 20 minutes, PhN(Tf)₂ (1.2 g, 3.5 mmol) was added. The reaction gradually turned red and was stirred for another hour. The mixture was concentrated and purified by silica gel chromatography to afford 1.077g of **66.38D** as a colorless oil (97%).

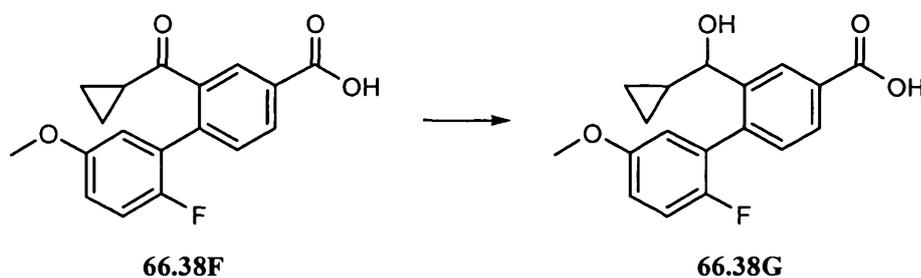


[0709] Methyl 3-(cyclopropanecarbonyl)-4-(2-fluoro-5-methoxyphenyl)benzoate (66.38E). Methyl 3-(cyclopropanecarbonyl)-4-(trifluoromethylsulfonyloxy)benzoate (**66.38D**) (1.077g, 3.1 mmol) was dried under

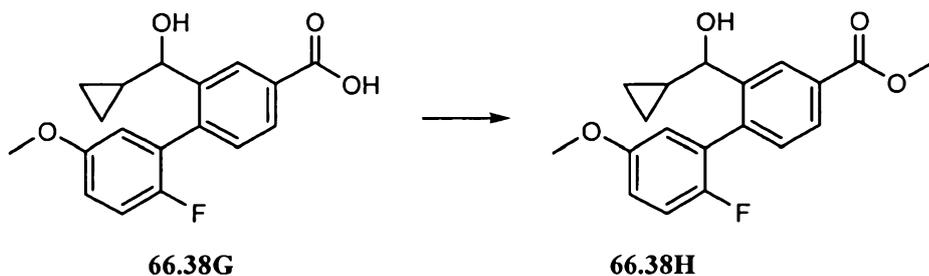
vacuum. To a second flask was added 2-fluoro-5-methoxyphenylboronic acid (1.5 g, 8.9 mmol)(commercially available from Aldrich), cesium carbonate (3.5 g, 11 mmol), and tetrakis(triphenylphosphine)Palladium (0) (0.35 g, 0.31 mmol). Both flasks were flushed with nitrogen followed by vacuum. Degassed DME was then added to the flask with **66.38D** (3 mL). Another 17 mL DME was added to the flask with the palladium catalyst followed by the DME solution of **66.38D**. The resulting slurry was stirred overnight in a 95°C oil-bath. The reaction was filtered, concentrated, and purified by silica gel chromatography to afford 0.94g of the desired product **66.38E** (94%).



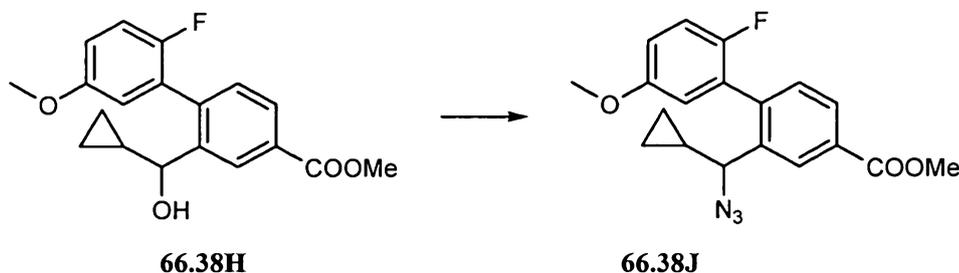
[0710] **3-(Cyclopropanecarbonyl)-4-(2-fluoro-5-methoxyphenyl)benzoic acid (66.38F)**. To a flask with methyl 3-(cyclopropanecarbonyl)-4-(2-fluoro-5-methoxyphenyl)benzoate (**66.38E**) (523 mg, 1593 μ mol) was added 9.6 mL of MeOH and 1N NaOH (3186 μ L, 3186 μ mol). The reaction was heated to 55 C for 2 hours. The mixture was then acidified with 1N HCl, concentrated, and extracted with EtOAc. Removal of the solvent afforded 500 mg of **66.38F** (100%).



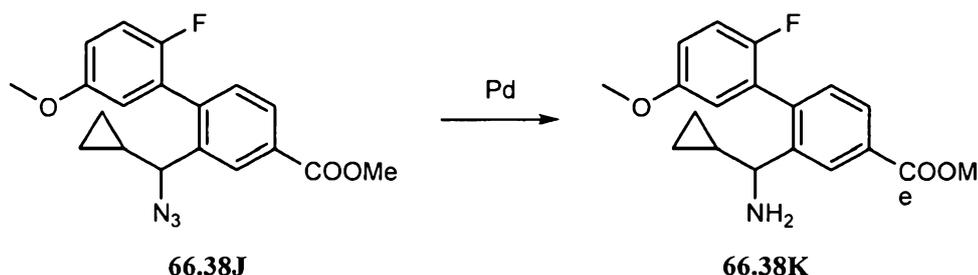
[0711] **3-(Cyclopropyl(hydroxy)methyl)-4-(2-fluoro-5-methoxyphenyl)benzoic acid (66.38G)**. To a flask with 3-(cyclopropanecarbonyl)-4-(2-fluoro-5-methoxyphenyl)benzoic acid (**66.38F**) (500 mg, 1591 μ mol) was added anhydrous EtOH 10 mL, followed by addition of sodium borohydride (361 mg, 0.95 mmol). The reaction mixture was stirred overnight, quenched with water, and extracted with EtOAc. Removal of solvent gave 503 mg of **66.38G** in racemic form.



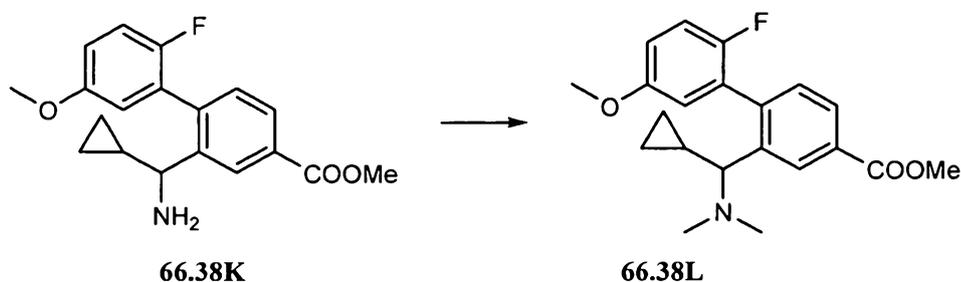
[0712] **Methyl 3-(cyclopropyl(hydroxy)methyl)-4-(2-fluoro-5-methoxyphenyl)benzoate (66.38H)**. To a flask with 3-(cyclopropyl(hydroxy)methyl)-4-(2-fluoro-5-methoxyphenyl)benzoic acid (**66.38G**), (503 mg, 1.6 mmol) was added 10 mL DCM and 2 mL MeOH. TMSdiazomethane (795 μ L, 1590 μ mol) in ether was then added, and the reaction was stirred at room temperature for 1 hour, and then quenched with a acetic acid. Water was added, and the reaction was extracted with EtOAc. Purification by silica gel chromatography afforded 484 mg of **66.38H** (92%) in racemic form.



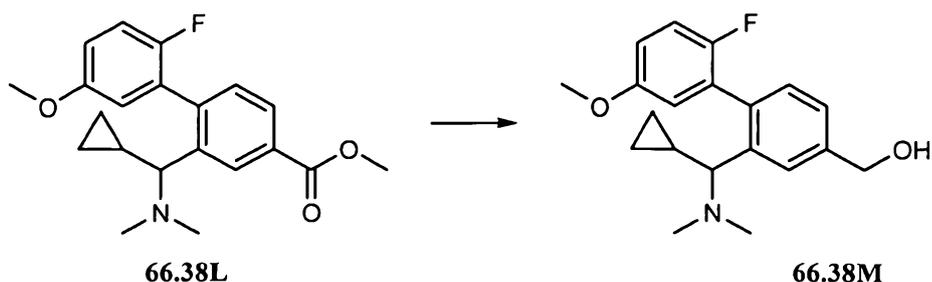
[0713] **Methyl 3-(azido(cyclopropyl)methyl)-4-(2-fluoro-5-methoxyphenyl)benzoate (66.38J)**. To methyl 3-(cyclopropyl(hydroxy)methyl)-4-(2-fluoro-5-methoxyphenyl)benzoate (**66.38H**) (235 mg, 711 μ mol) was added DMF 4 mL, then 1,8-diazabicyclo[5.4.0]undec-7-ene (160 μ L, 1067 μ mol), and diphenylphosphoryl azide (231 μ L, 1067 μ mol). The mixture was heated to 80°C. After 3 hours, 1.5 equivalents more of each of the 1,8-diazabicyclo[5.4.0]undec-7-ene and diphenylphosphoryl azide were added. The reaction was heated for two more hours and water was then added followed by EtOAc extraction. Purification by silica gel chromatography afforded 260 mg of **66.38J** mixed with a non-polar side product. The product thus obtained was carried to the next step without further purification.



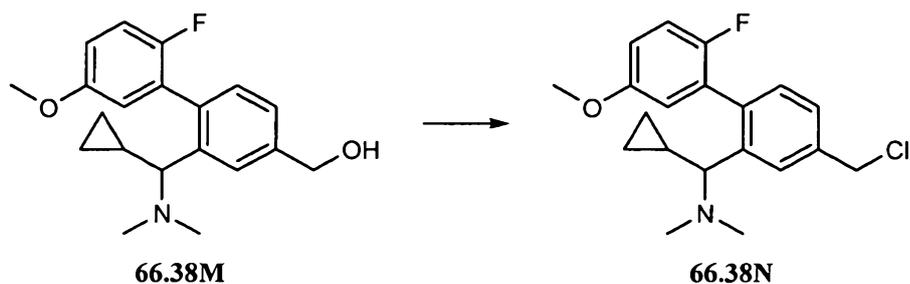
[0714] Methyl 3-(amino(cyclopropyl)methyl)-4-(2-fluoro-5-methoxyphenyl)benzoate (66.38K). To a flask with methyl 3-(azido(cyclopropyl)methyl)-4-(2-fluoro-5-methoxyphenyl)benzoate (**66.38J**) (260 mg, 732 μmol) was added 10% Pd/C (78 mg, 732 μmol), and then 6 mL of MeOH was added. The reaction was purged with hydrogen and stirred under a hydrogen balloon for about 6 hours. The reaction was filtered through a pad of Celite filter aid, concentrated, and purified by silica gel chromatography to afford 76 mg of the desired product **66.38K** (32% for 2 steps).



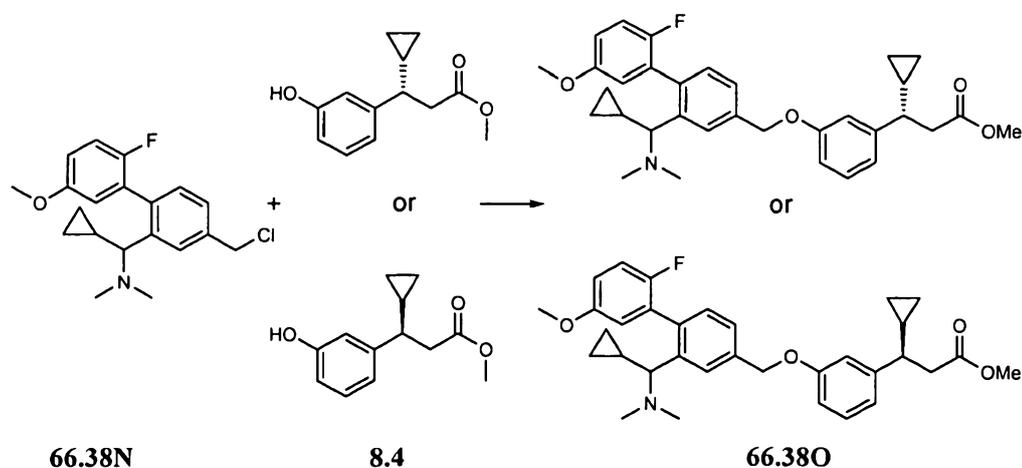
[0715] Methyl 3-(cyclopropyl(dimethylamino)methyl)-4-(2-fluoro-5-methoxyphenyl)benzoate (66.38L). To a flask with methyl 3-(amino(cyclopropyl)methyl)-4-(2-fluoro-5-methoxyphenyl)benzoate (**66.38K**) (76 mg, 231 μmol) were added 2 mL DCM, formaldehyde (70 μL , 923 μmol), and acetic acid (26 μL , 461 μmol). Sodium triacetoxyborohydride (245 mg, 1154 μmol) was then added to the reaction mixture. The reaction was stirred for 1.5 hours and worked up with water and EtOAc. Silica gel chromatography afforded 35 mg of **66.38L** (43%).



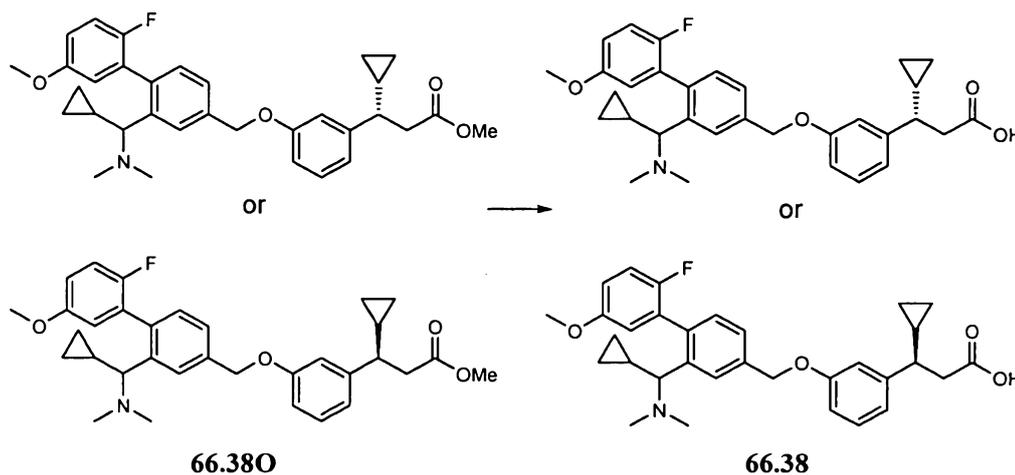
[0716] (3-(Cyclopropyl(dimethylamino)methyl))-4-(2-fluoro-5-methoxyphenyl)phenyl)methanol (66.38M). To a flask with methyl 3-(amino(cyclopropyl)methyl)-4-(2-fluoro-5-methoxyphenyl)benzoate (**66.38K**) (35 mg, 98 μ mol) was added THF (1.5 mL). The mixture was cooled to 0°C and then 1M LAH (196 μ L, 196 μ mol, 1M solution in THF) was added. The temperature was slowly raised to room temperature over 1 hour. Water and a small amount of Rochelle's salt solution were added to quench the reaction and it was then extracted with EtOAc. Silica gel chromatography afforded 26 mg of **66.38M** (81%).



[0717] (5-(Chloromethyl)-2-(2-fluoro-5-methoxyphenyl)phenyl)(cyclopropyl)-N,N-dimethylmethanamine (66.38N). To a flask with (3-(cyclopropyl(dimethylamino)methyl))-4-(2-fluoro-5-methoxyphenyl)phenyl)methanol (**66.38M**) (26 mg, 79 μ mol) was added DCM. The mixture was cooled in an ice-bath and then thionyl chloride (12 μ L, 158 μ mol) and DMF (6 μ L, 79 μ mol) were added. The reaction was stirred at room temperature for 1 hour, and then it was concentrated and purified by silica gel chromatography to afford 28 mg of **66.38N** (102%).

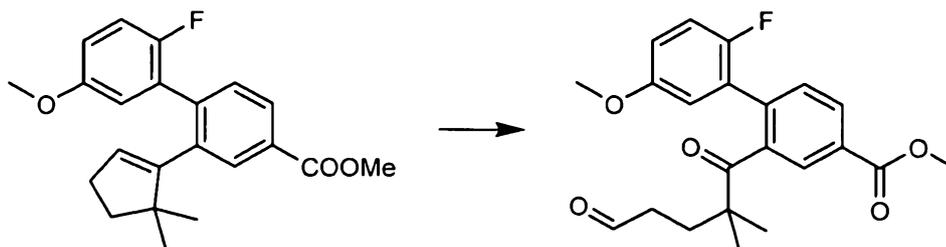


[0718] (3S)-Methyl 3-cyclopropyl-3-(3-(((2-(cyclopropyl(dimethylamino)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or (3R)-methyl 3-cyclopropyl-3-(3-(((2-(cyclopropyl(dimethylamino)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.38O). To a flask with 66.38N (28 mg, 80 μ mol), was added 8.4 (21 mg, 97 μ mol), and cesium carbonate (39 mg, 121 μ mol). DMF (1.2 mL) was then added to the mixture. The reaction was stirred for 16 hours and worked up with water and EtOAc. Silica gel chromatography afforded 43 mg of 66.38O (100%).



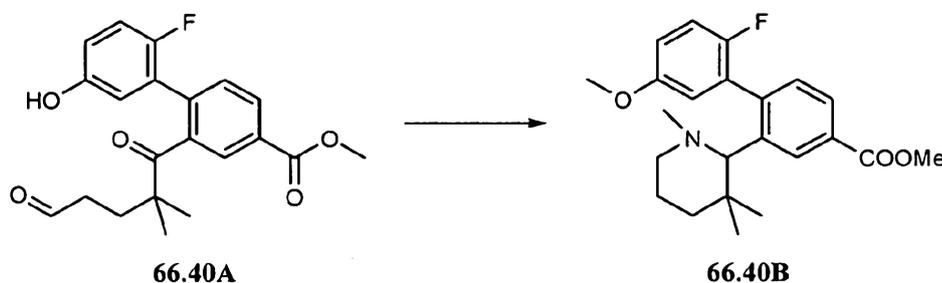
[0719] (3S)-3-Cyclopropyl-3-(3-(((2-(cyclopropyl(dimethylamino)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-(cyclopropyl(dimethylamino)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.38). To a flask with 66.38O (43 mg) was added 1 mL THF (0.5 mL), MeOH (0.5 mL) and LiOH. The reaction was stirred overnight, neutralized with 1N HCl, and extracted with EtOAc. The reaction was purified by silica gel chromatography to afford 8 mg of 66.38 (19%) as 1:1 ratio of diastereomers. MS ESI (pos.) m/e: 518.2 (M+H)⁺.

[0720] **Example 66.40**

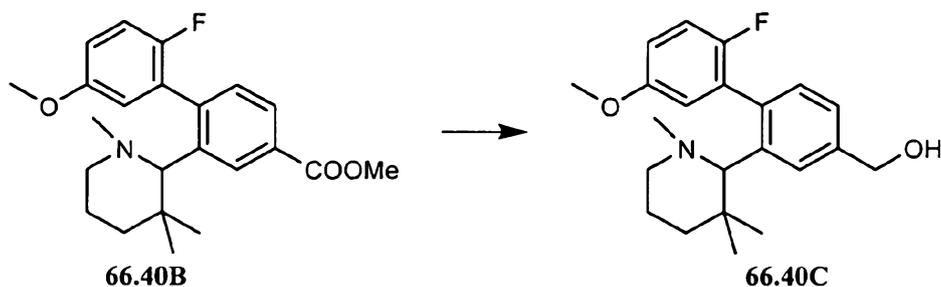


66.6J**66.40A**

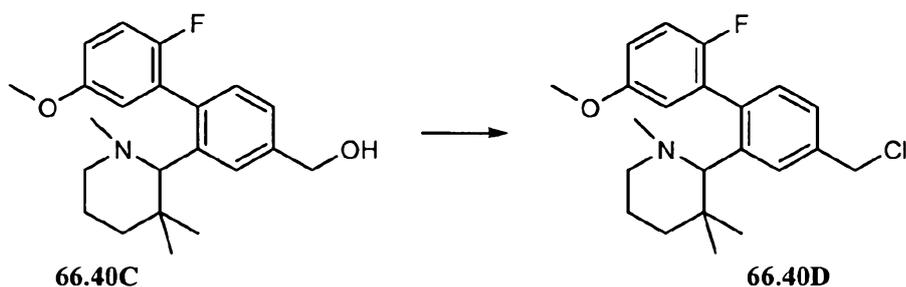
[0721] **2'-Fluoro-5'-methoxy-2-(5-oxo-pentanoyl)-biphenyl-4-carboxylic acid methyl ester (66.40A)**. To a solution of 2-(5,5-Dimethyl-cyclopent-1-enyl)-2'-fluoro-5'-methoxy-biphenyl-4-carboxylic acid methyl ester **66.6J** (0.10 g, 0.28 mmol) in a mixed solvent of MeOH and DCM (3/1) at -78°C, was slowly bubbled O₃ for 5 minutes. Dimethylsulfane (0.052g, 0.84mmol) was added to the solution, and the resulting mixture was warmed to room temperature and stirred for 16 hours. The solvent was evaporated, and the residue was purified by silica gel chromatography (eluent was EtOAc and hexane) to give **66.40A**. ¹H NMR (CDCl₃) δ ppm 1.01 (s, 6 H), 1.77 (t, J = 8.0 Hz, 2 H), 2.21 (t, J = 8.0 Hz, 2 H), 3.79 (s, 3 H), 3.98 (s, 3H), 6.79 (m, 1H), 6.90 (m, 1H), 7.07 (t, J = 8.0 Hz, 1 H), 7.51 (d, J = 8.0 Hz, 1 H), 7.94 (s, 1H), 8.12 (d, J = 8.0 Hz, 1 H), 9.67(s, 1H).



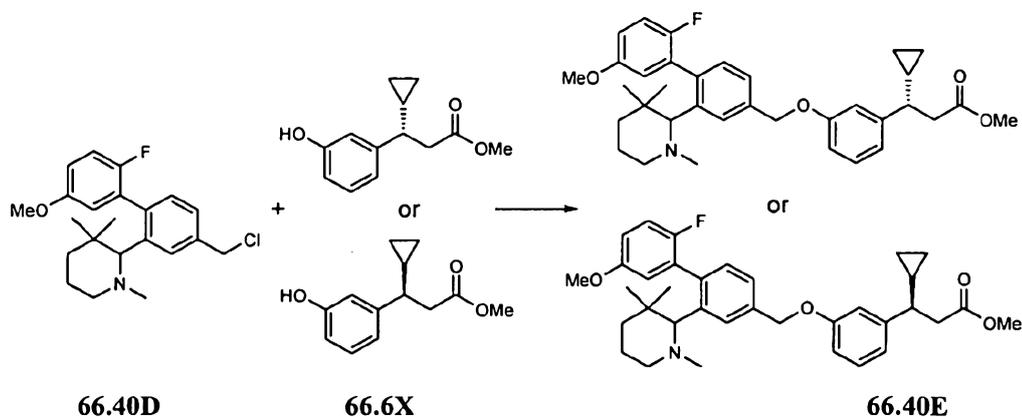
[0722] **2'-Fluoro-5'-methoxy-2-(1,3,3-trimethyl-piperidin-2-yl)-biphenyl-4-carboxylic acid methyl ester (66.40B)**. To a solution of **66.40B** (45 mg, 116 μmol) in EtOH, was added methylamine (33% wt solution in absolute EtOH) (146 μL, 1165 μmol) and acetic acid (70mg, 1165 μmol). The resulting mixture was stirred at room temperature for 10 minutes and then sodium cyanoborohydride (15 μL, 291 μmol) was added. The mixture was stirred at room temperature for 2 hours and then heated at reflux for 16 hours. Solvent was removed, and the reaction mixture was diluted with EtOAc. The organic phase was washed carefully with saturated aqueous NaHCO₃, once with brine, and then dried over anhydrous sodium sulfate. After filtration, the organic solvent was removed in vacuo to yield **66.40B** (36mg) which was used without purification.



[0723] **[2'-Fluoro-5'-methoxy-2-(1,3,3-trimethyl-piperidin-2-yl)-biphenyl-4-yl]-methanol (66.40C)** Compound 66.40C was synthesized by a method analogous to the method used for synthesizing compound 8.9 from 8.8. MS ESI m/e : 358.2 (M+H)⁺.

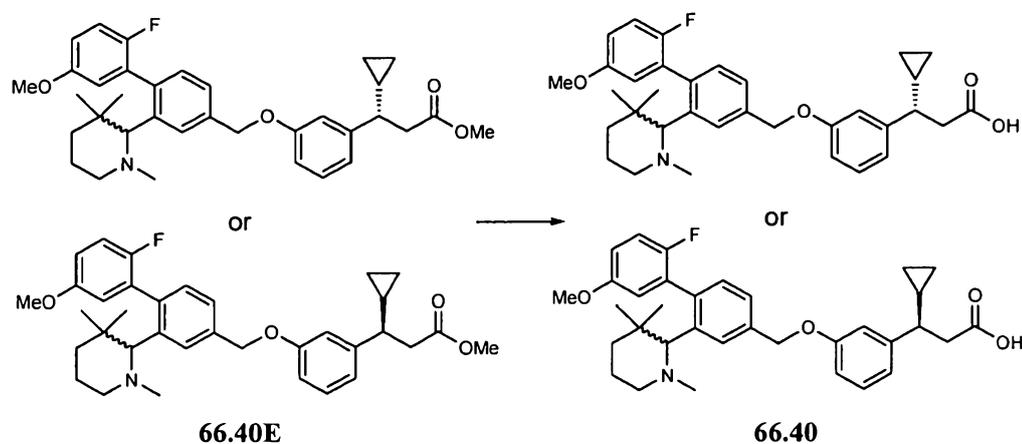


[0724] **2-(4-Chloromethyl-2'-fluoro-5'-methoxy-biphenyl-2-yl)-1,3,3-trimethyl-piperidine (66.40D)** Compound 66.40D was synthesized by a method analogous to the method used to prepare compound 8.10 from 8.9. MS ESI m/e : 376.2 (M+H)⁺.



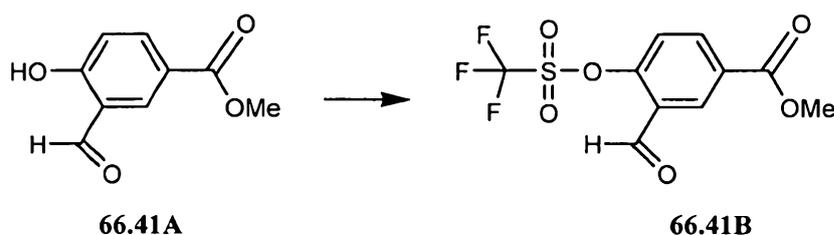
[0725] **(S)-3-Cyclopropyl-3-{3-[2'-fluoro-5'-methoxy-2-(1,3,3-trimethyl-piperidin-2-yl)-biphenyl-4-ylmethoxy]-phenyl}-propionic acid methyl ester or (R)-3-Cyclopropyl-3-{3-[2'-fluoro-5'-methoxy-2-(1,3,3-trimethyl-piperidin-2-yl)-biphenyl-4-ylmethoxy]-phenyl}-propionic acid methyl ester (66.40E)**. Compound 66.40E was

synthesized using a method analogous to the method used for compound to prepare compound **66.13P** from **66.40E** and **66.6X**. MS ESI m/e: 560.3 (M+H)⁺.



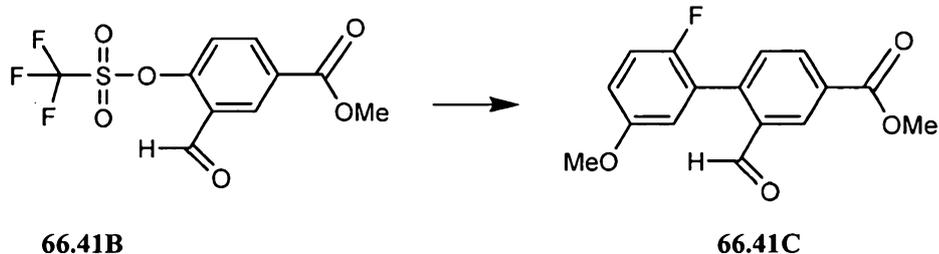
[0726] **(S)-3-Cyclopropyl-3-{3-[2'-fluoro-5'-methoxy-2-(1,3,3-trimethyl-piperidin-2-yl)-biphenyl-4-ylmethoxy]-phenyl}-propionic acid or (R)-3-cyclopropyl-3-{3-[2'-fluoro-5'-methoxy-2-(1,3,3-trimethyl-piperidin-2-yl)-biphenyl-4-ylmethoxy]-phenyl}-propionic acid (**66.40**)**. Compound **66.40** was synthesized by a method analogous to the method used to prepare compound **66.13** from **66.13P**. MS ESI m/e: 546.3 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.65 (m, 1H), 7.53 (m, 1H), 7.38 (m, 1H), 7.20 (m, 2H), 7.05 (m, 1H), 6.80-6.89 (m, 4H), 5.26 (s, 2H), 4.14 (s, 0.3H), 3.91 (s, 0.7H), 3.84 (s, 1.2H), 3.79 (s, 1.8H), 3.65 (m, 1H), 3.15 (m, 1H), 2.74 (m, 2H), 2.69 (d, J = 4Hz, 2.3H), 2.65 (s, 0.7H), 2.30 (m, 1H), 2.03 (m, 1H), 1.82 (m, 1H), 1.60 (m, 1H), 1.42 (m, 1H), 1.02 (m, 1H), 0.96 (d, J = 4Hz, 3H), 0.55 (m, 4H), 0.37 (m, 1H), 0.27 (m, 1H), 0.09 (m, 1H).

[0727] **Example 66.41**

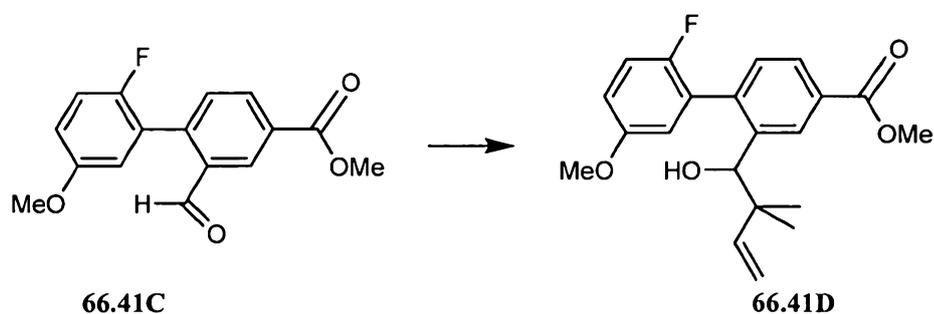


[0728] Methyl 3-formyl-4-(trifluoromethylsulfonyloxy)benzoate (66.41B).

Compound **66.41B** was synthesized from methyl 3-formyl-4-hydroxybenzoate **66.41A** (commercially available from Aldrich) using a method analogous to the method used to prepare compound **66.6I** from **66.6H**. MS ESI m/e : 313.2 (M+H)⁺.

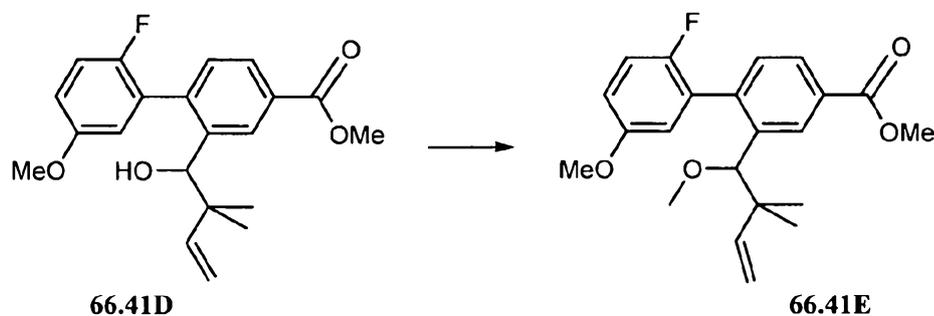
**[0729] 2'-Fluoro-2-formyl-5'-methoxy-biphenyl-4-carboxylic acid methyl ester (66.41C).**

To a round bottle flask, was added methyl 3-formyl-4-(trifluoromethylsulfonyloxy)benzoate (6300 mg, 20 mmol), 2-fluoro-5-methoxyphenylboronic acid (10 g, 61 mmol)(commercially available from Aldrich), potassium phosphate tribasic (6.6 mL, 81 mmol) (granular) and tetrakis(triphenylphosphine)palladium (2.3 g, 2.0 mmol). The flask was flushed with nitrogen, DME was added, and the mixture was heated at 90°C for 6 hours. The reaction mixture was diluted with EtOAc and water. The organic phase was washed with water and brine and then dried over anhydrous sodium sulfate. After filtration, the organic solvent was removed in vacuo to give a residue which was purified by chromatography to give the product as a yellow solid (5.80g, 100%). MS ESI m/e : 289.2 (M+H)⁺.

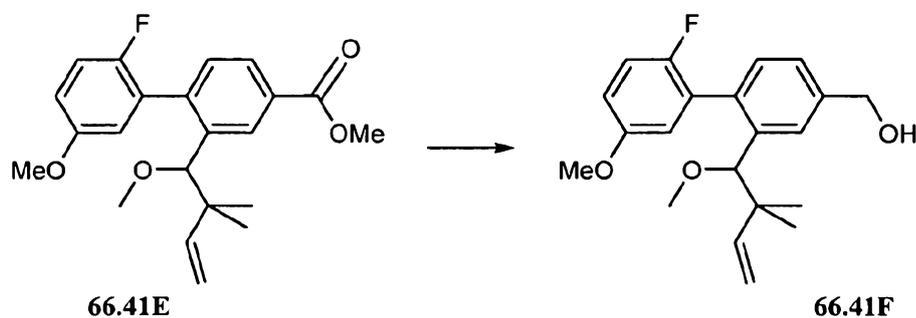
**[0730] 2'-Fluoro-2-(1-hydroxy-2,2-dimethyl-but-3-enyl)-5'-methoxy-**

biphenyl-4-carboxylic acid methyl ester (66.41D). To a mixed solution of sodium iodide (2080 mg, 13876 μ mol), indium (2000mg, 6938 μ mol) and 1-bromo-3-methylbut-2-ene (1616 μ L, 13876 μ mol) in DMF(30 mL), was added **66.41C** (1593 mg, 13876 μ mol). The mixture was stirred at room temperature for 1 hour, and then was diluted with

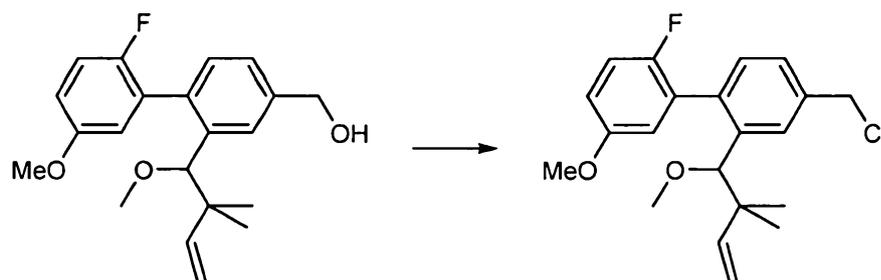
EtOAc and water. The organic phase was washed with water and brine and then dried over anhydrous sodium sulfate. After filtration, the organic solvent was removed in vacuo to give a residue which was purified by chromatography to give the product as an oil (2.30g, 92%). MS ESI m/e : 376.1 (M+18)⁺.



[0731] 2'-Fluoro-5'-methoxy-2-(1-methoxy-2,2-dimethyl-but-3-enyl)-biphenyl-4-carboxylic acid methyl ester (66.41E). To a solution of **66.41D** (1530 mg, 4269 μmol) in DMF (40 mL), was added sodium hydride (60% in oil)(213 μL , 8538 μmol). The mixture was stirred at room temperature for 10 minutes and then methyl iodide (530 μL , 8538 μmol) was added in one portion and the mixture was stirred at room temperature for 30 minutes. Water was added and the mixture was, extracted with EtOAc. The organic phase was washed with water and brine and then dried over anhydrous sodium sulfate. After filtration, the organic solvent was removed in vacuo to give the product as a residue which was purified by chromatography to give the product as an oil (0.75g, 47%). MS ESI m/e : 373.2 (M+18)⁺.



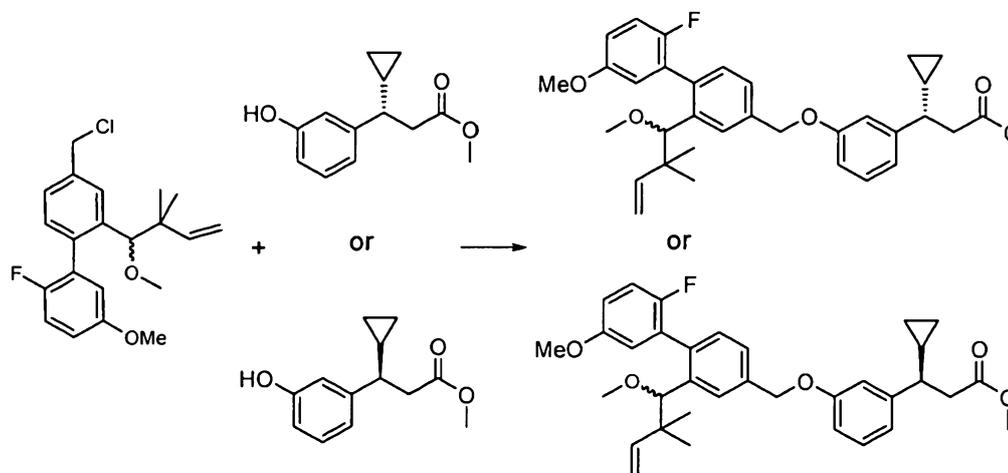
[0732] [2'-Fluoro-5'-methoxy-2-(1-methoxy-2,2-dimethyl-but-3-enyl)-biphenyl-4-yl]-methanol (66.41F). Compound **66.41F** was synthesized from **66.41E** by a method analogous to that used to prepare compound **8.9** from **8.8**. MS ESI m/e : 345.2 (M+H)⁺.



66.41F

66.41G

[0733] **4-Chloromethyl-2'-fluoro-5'-methoxy-2-(1-methoxy-2,2-dimethyl-but-3-enyl)-biphenyl (66.41G).** Compound 66.41G was synthesized by a method analogous to the method used to prepare compound 8.10 from 8.9. MS ESI m/e : 363.2 $(M+H)^+$.

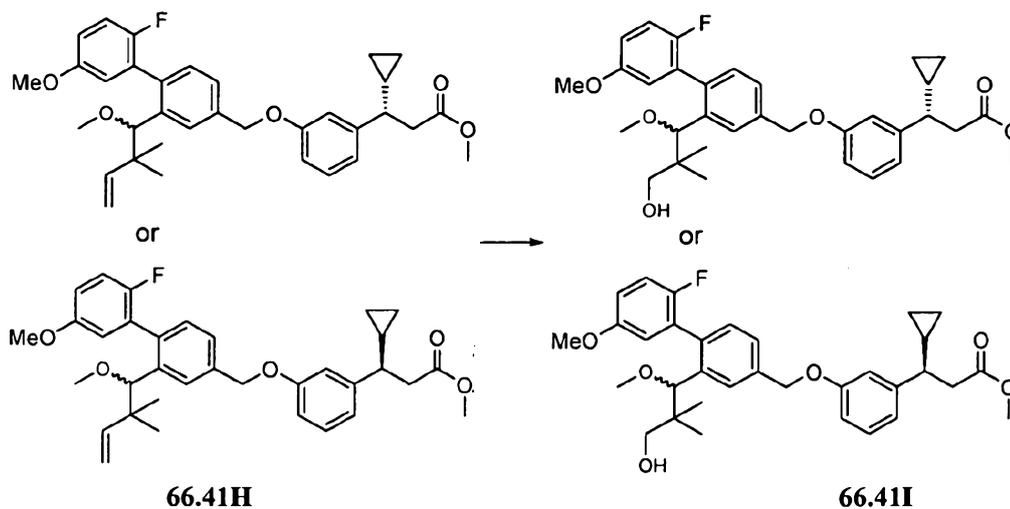


66.41G

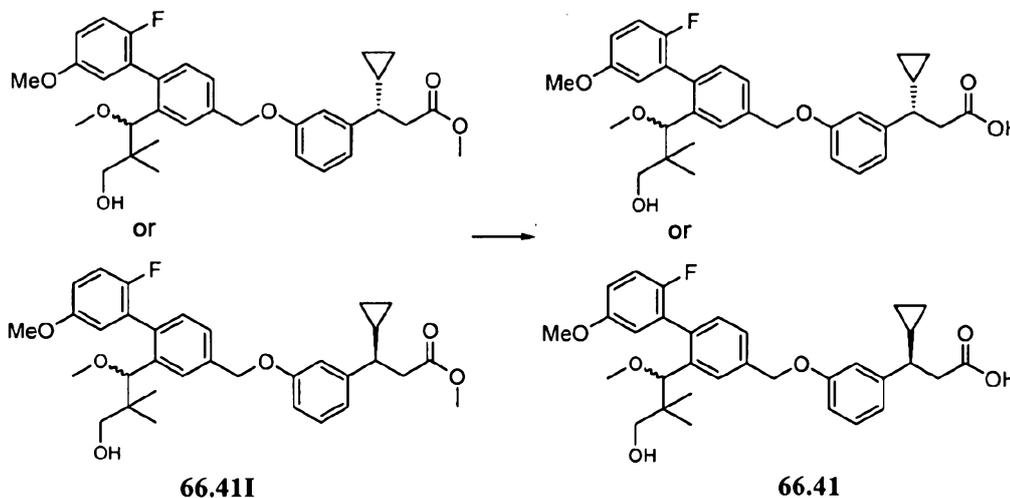
66.6X

66.41H

[0734] **(R)-3-{3-[2'-Fluoro-5'-methoxy-2-(1-methoxy-2,2-dimethyl-but-3-enyl)-biphenyl-4-ylmethoxy]-phenyl}-pentanoic acid methyl ester or (S)-3-{3-[2'-fluoro-5'-methoxy-2-(1-methoxy-2,2-dimethyl-but-3-enyl)-biphenyl-4-ylmethoxy]-phenyl}-pentanoic acid methyl ester (66.41H).** Compound 66.41H was synthesized from 66.41G and 66.6X using a method analogous to the method used to prepare compound 66.13P. MS ESI m/e : 547.3 $(M+H)^+$.

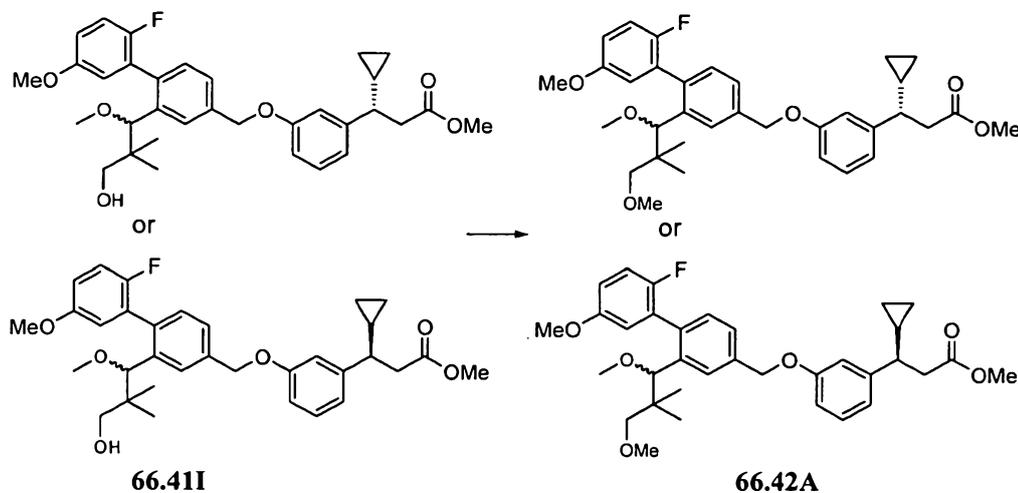


[0735] (S)-3-Cyclopropyl-3-{3-[2'-fluoro-2-(3-hydroxy-1-methoxy-2,2-dimethyl-propyl)-5'-methoxy-biphenyl-4-ylmethoxy]-phenyl}-propionic acid methyl ester or (R)-3-cyclopropyl-3-{3-[2'-fluoro-2-(3-hydroxy-1-methoxy-2,2-dimethyl-propyl)-5'-methoxy-biphenyl-4-ylmethoxy]-phenyl}-propionic acid methyl ester (**66.41I**). Into a solution of **66.41H** (303 mg, 554 μmol) at -78°C in DCM/methanol (1 mL/5 mL), was bubbled with O_3 for 3 minutes and then sodium borohydride (195 μL , 5543 μmol) was added. The mixture was stirred at room temperature for 16 hours and then solvent was removed and the reaction mixture was diluted with EtOAc. The organic phase was washed carefully with saturated aqueous NaHCO_3 , once with brine, and then dried over anhydrous sodium sulfate. After filtration, the organic solvent was removed in vacuo to yield **66.41I** that was used without purification. MS ESI m/e : 551.3 ($\text{M}+\text{H}$)⁺.

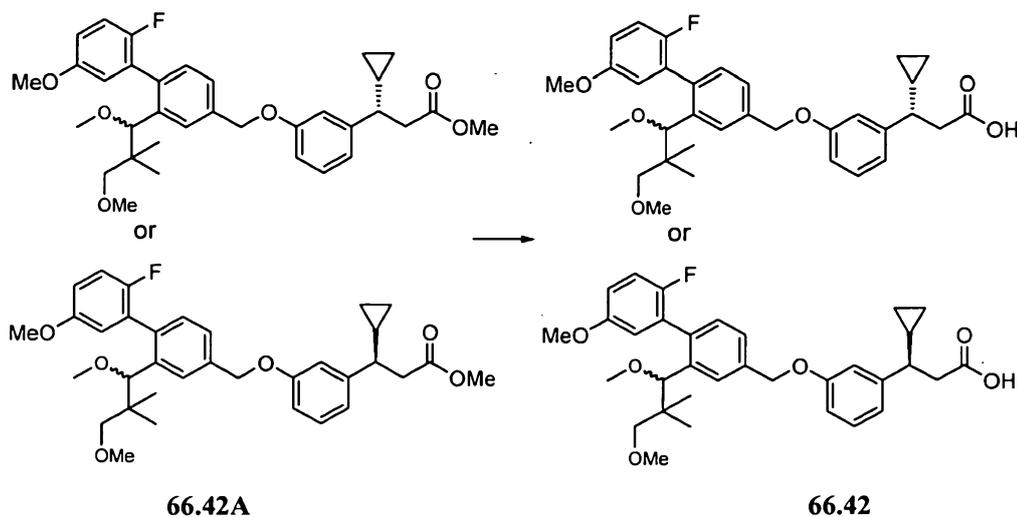


[0736] (S)-3-Cyclopropyl-3-{3-[2'-fluoro-2-(3-hydroxy-1-methoxy-2,2-dimethyl-propyl)-5'-methoxy-biphenyl-4-ylmethoxy]-phenyl}-propionic acid or (R)-3-cyclopropyl-3-{3-[2'-fluoro-2-(3-hydroxy-1-methoxy-2,2-dimethyl-propyl)-5'-methoxy-biphenyl-4-ylmethoxy]-phenyl}-propionic acid (66.41). Compound 66.41 was synthesized by a method analogous to the method used to prepare compound 66.13 from 66.13P. MS ESI m/e : 537.3 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.55 (m, 1H), 7.45 (m, 1H), 7.21 (m, 2H), 7.01 (m, 1H), 6.94 (m, 3H), 6.79 (m, 1H), 6.71 (m, 1H), 5.18 (s, 2H), 4.47 (s, 0.4H), 4.26 (s, 0.6H), 3.79 (s, 3H), 3.25 (m, 5H), 2.77 (m, 2H), 2.37 (m, 1H), 1.03 (m, 1H), 0.61 (m, 7H), 0.43 (m, 1H), 0.29 (m, 1H), 0.19 (m, 1H).

[0737] **Example 66.42**

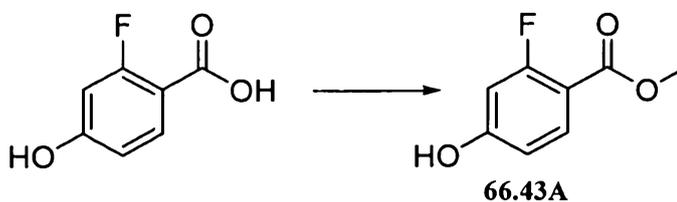


[0738] (S)-3-Cyclopropyl-3-{3-[2-(1,3-dimethoxy-2,2-dimethyl-propyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-phenyl}-propionic acid methyl ester or (R)-3-cyclopropyl-3-{3-[2-(1,3-dimethoxy-2,2-dimethyl-propyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-phenyl}-propionic acid methyl ester (66.42A). Compound 66.42A was synthesized by a method analogous to the method used to prepare compound 66.41E from 66.41D. MS ESI m/e : 565.3 (M+H)⁺.



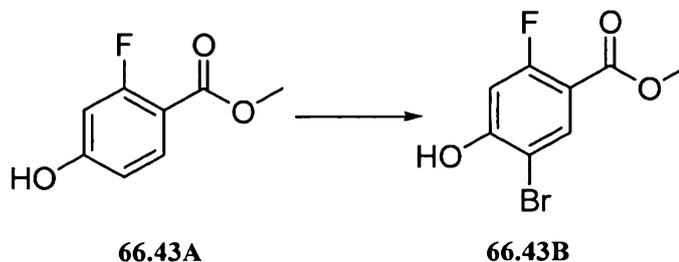
[0739] (S)-3-Cyclopropyl-3-{3-[2-(1,3-dimethoxy-2,2-dimethyl-propyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-phenyl}-propionic acid or (S)-3-Cyclopropyl-3-{3-[2-(1,3-dimethoxy-2,2-dimethyl-propyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-phenyl}-propionic acid (**66.42**). Compound **66.42** was synthesized using a method analogous to that used to prepare compound **66.13** from **66.13P**. MS ESI m/e : 551.3 (M+H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.57 (m, 1H), 7.42 (m, 1H), 7.20 (m, 2H), 7.01 (m, 1H), 6.86 (m, 4H), 6.74 (m, 1H), 5.15 (s, 2H), 4.41 (s, 0.3H), 4.19 (s, 0.7H), 3.78 (s, 3H), 3.19 (m, 7H), 2.96 (m, 1H), 2.78 (m, 2H), 2.36 (m, 1H), 1.01 (m, 1H), 0.74 (s, 3H), 0.56 (m, 4H), 0.41 (m, 1H), 0.28 (m, 1H), 0.17 (m, 1H).

[0740] **Example 66.43**

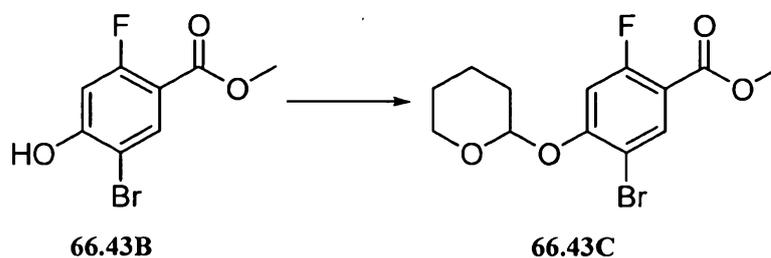


[0741] **Methyl 2-fluoro-4-hydroxybenzoate (66.43A)**. To a round bottom containing 2-fluoro-4-hydroxybenzoic acid (5.34 g, 34.19 mmol) (commercially available from Matrix Scientific and TCI America) was added a cold solution of MeOH (50 mL) and sulfuric acid (2.0 mL). The mixture was heated to 80°C and monitored with TLC. After 20.5 hours, the solvent was removed, and the mixture was diluted with diethyl ether. The organic phase was washed carefully two times with saturated, aqueous

NaHCO₃, once with brine, and then dried over anhydrous sodium sulfate. After filtration, the organic solvent was removed in vacuo to yield **66.43A** as a white solid (5.82, 85% yield). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.79 (1 H, s), 7.75 (1 H, t, J=8.8 Hz), 6.69 (1 H, dd, J=8.6, 2.3 Hz), 6.62 (1 H, dd, J=13.1, 2.2 Hz), 3.78 (3 H, s).

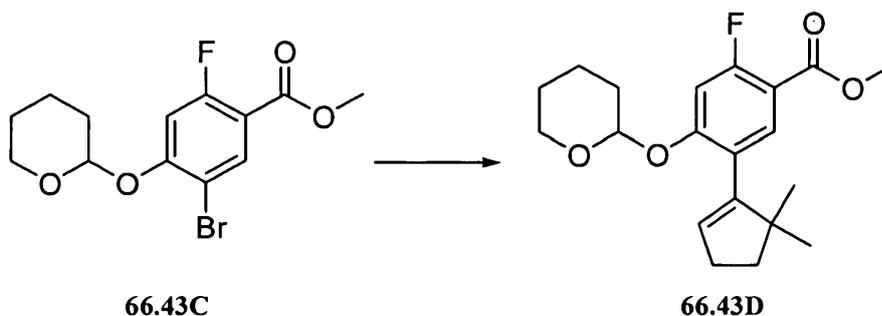


[0742] Methyl 5-bromo-2-fluoro-4-hydroxybenzoate (66.43B). To a solution of **66.43A** (2.03 g, 11.9 mmol) in acetic acid (65 mL) was added a pre-mixed solution of bromine (0.67 mL, 13.1 mmol) in acetic acid (10 mL). The mixture was stirred at 45°C and monitored with TLC and LC-MS. After 18 hours, the reaction mixture was concentrated under reduced pressure. Brine was added to the residue, and the mixture was extracted three times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated to provide **66.43B** as a white solid (2.12 g, 71 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.13 (1 H, d, J=7.4 Hz), 6.82 (1 H, d, J=11.3 Hz), 6.04 (1 H, s), 3.92 (3 H, s).

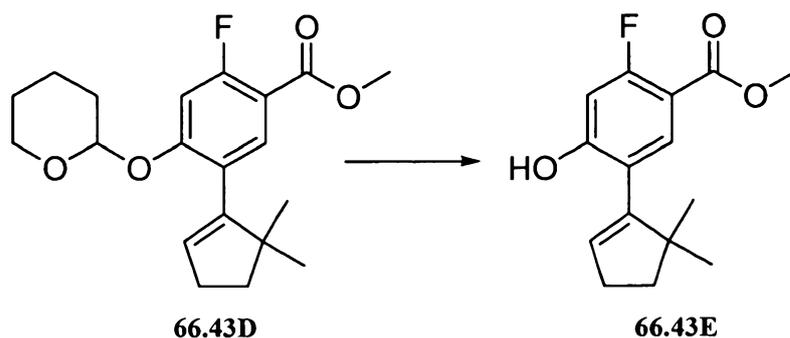


[0743] Methyl 5-bromo-2-fluoro-4-(tetrahydro-2H-pyran-2-yloxy)benzoate (66.43C). To a round bottom containing **66.43B** (13.15 g, 52.8 mmol) in dry DCM (90 mL) was added 3,4-dihydro-2H-pyran (10 mL, 110 mmol) followed by PPTS (0.13 g, 0.53 mmol). The reaction mixture was heated to a gentle reflux (50 °C) and monitored with TLC and LC-MS. After 24 hours, the reaction was concentrated under reduced pressure and then diluted with MeOH. After concentration, the residue was heated in a round bottom flask containing MeOH on the rotary evaporator (without vacuum.) at 40°C.

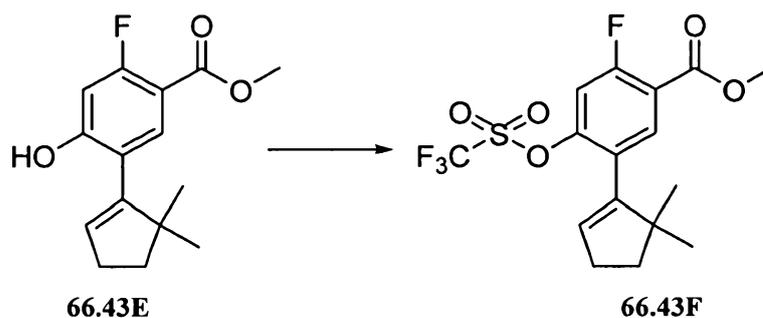
After about 30 minutes, the solution was concentrated to a volume of about 5 mL. After cooling to room temperature, the white solid was filtered and rinsed once with MeOH to yield **66.43C** (13.35 g, 76 % yield). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 8.25 (1 H, m), 6.96 (1 H, d, $J=12.5$ Hz), 5.56 (1 H, m), 3.91 (3 H, s), 3.79 (1 H, td, $J=11.1, 2.5$ Hz), 3.65 (1 H, d, $J=10.6$ Hz), 2.23 (2 H, m), 1.96 (3 H, m), 1.68 (1 H, m).



[0744] Methyl 5-(5,5-dimethylcyclopent-1-enyl)-2-fluoro-4-(tetrahydro-2H-pyran-2-yloxy)benzoate (66.43D). A stirred mixture of **66.43 C** (10.33 g, 31.0 mmol), ground S-Phos (2.55 g, 6.21 mmol), palladium acetate (0.70 g, 3.11 mmol), and potassium phosphate, tribasic (16.49 g, 77.7 mmol) in DMF (75 mL) and water (4 mL) was purged with argon and placed under vacuum and the process repeated three times. Before heating, 2-(5,5-dimethylcyclopent-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**66.6 C**) (8.96 g, 40.4 mmol) was added via syringe. The mixture was then heated at 75°C. After 21 hours, the reaction was cooled to room temperature, diluted with water, and extracted three times with EtOAc. The organic layers were combined and washed twice with brine. After drying over anhydrous sodium sulfate and filtration, the organic solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to yield **66.43D** (5.65 g, 52 % yield). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 7.63 (1 H, d, $J=8.6$ Hz), 6.93 (1 H, d, $J=13.3$ Hz), 5.55 (1 H, t, $J=2.3$ Hz), 5.43 (1 H, t, $J=2.7$ Hz), 3.90 (3 H, s), 3.82 (1 H, m), 3.67 (1 H, m), 2.41 (2 H, td, $J=7.0, 2.3$ Hz), 1.97 (5 H, m), 1.79 (3 H, m), 1.07 (6 H, d, $J=13.7$ Hz).

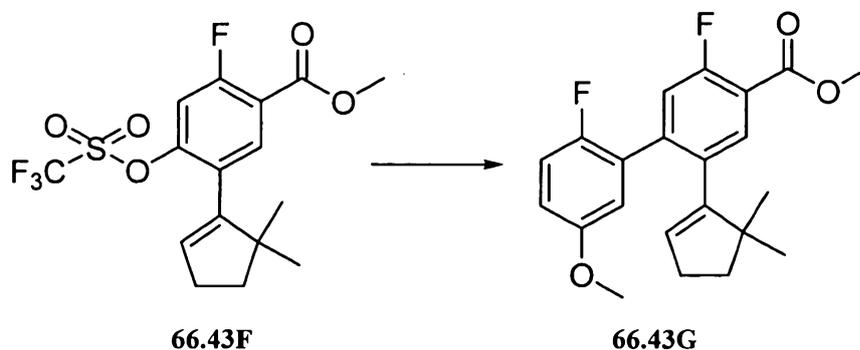


[0745] **Methyl 5-(5,5-dimethylcyclopent-1-enyl)-2-fluoro-4-hydroxybenzoate (66.43E).** To a stirred mixture of **66.43D** (5.65 g, 16.2 mmol) in MeOH (60 mL) was added PPTS (0.42 g, 1.69 mmol). The mixture was heated to 50 °C and monitored with TLC and LCMS. After 19 hours, the organic solvent was removed under reduced pressure, and the residue was then purified on silica gel (0-15% EtOAc in hexanes) to yield **66.43E** as a white solid (3.47g, 81% yield). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.69 (1 H, d, J=8.3 Hz), 6.71 (1 H, d, J=12.0 Hz), 5.93 (1 H, d, J=1.7 Hz), 5.80 (1 H, t, J=2.4 Hz), 3.90 (3 H, s), 2.54 (2 H, m), 1.93 (2 H, t, J=7.1 Hz), 1.11 (6 H, s).

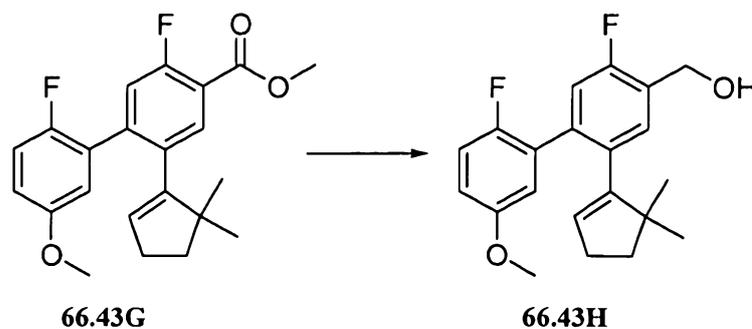


[0746] **Methyl 5-(5,5-dimethylcyclopent-1-enyl)-2-fluoro-4-(trifluoromethylsulfonyloxy)benzoate (66.43F).** To a stirred solution of **66.43E** (0.80 g, 3.02 mmol) in dry DCM (15 mL) was added TEA (1.0 mL, 7.19 mmol) and 4-dimethylaminopyridine (38.1 mg, 0.312 mmol). After about 20 minutes, N-phenyl-bis(trifluoromethanesulfonimide) (1.30 g, 3.64 mmol) was added in portions. Upon complete addition, the solution was stirred at room temperature and monitored with TLC and LC-MS. After 19 hours, the organic solvent was removed under reduced pressure and the resulting residue was purified with silica gel chromatography using 0-10% EtOAc in hexanes to yield **66.43F** as a colorless oil (1.05 g, 88% yield). ¹H NMR (400 MHz,

CDCl₃) δ ppm 7.84 (1 H, d, J=7.8 Hz), 7.13 (1 H, d, J=10.2 Hz), 5.79 (1 H, t, J=2.3 Hz), 3.96 (3 H, s), 2.47 (2 H, td, J=7.0, 2.3 Hz), 1.91 (2 H, t, J=7.0 Hz), 1.08 (6 H, s).

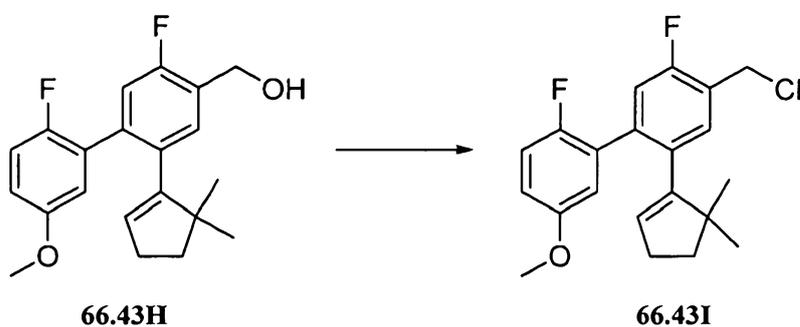


[0747] **Methyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.43G).** To a stirred solution of **66.43F** (1.05 g, 2.65 mmol) in DMF (5 mL) at 23 °C was added 2-fluoro-5-methoxyphenylboronic acid (0.90 g, 5.32 mmol) (commercially available from Aldrich) and potassium carbonate (1.10 g, 7.96 mmol) followed by tetrakis(triphenylphosphine)palladium (0.31 g, 0.27 mmol). The mixture was heated to 90 °C. After 17 hours, the mixture was cooled to room temperature and then diluted with water. After extracting three times with EtOAc, the mixture was concentrated in vacuo and then purified on silica gel (0%-10% EtOAc/hexane) to give **66.43G** as a clear oil that was used without further purification (0.92 g, 93 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.79 (1 H, d, J=7.4 Hz), 7.13 (1 H, d, J=11.3 Hz), 6.99 (1 H, t, J=9.0 Hz), 6.84 (1 H, dt, J=8.7, 3.7 Hz), 6.78 (1 H, dd, J=5.9, 3.1 Hz), 5.55 (1 H, s), 3.96 (3 H, s), 3.79 (3 H, s), 2.27 (2 H, td, J=7.1, 2.5 Hz), 1.67 (2 H, t, J=7.0 Hz), 0.84 (6 H, s).

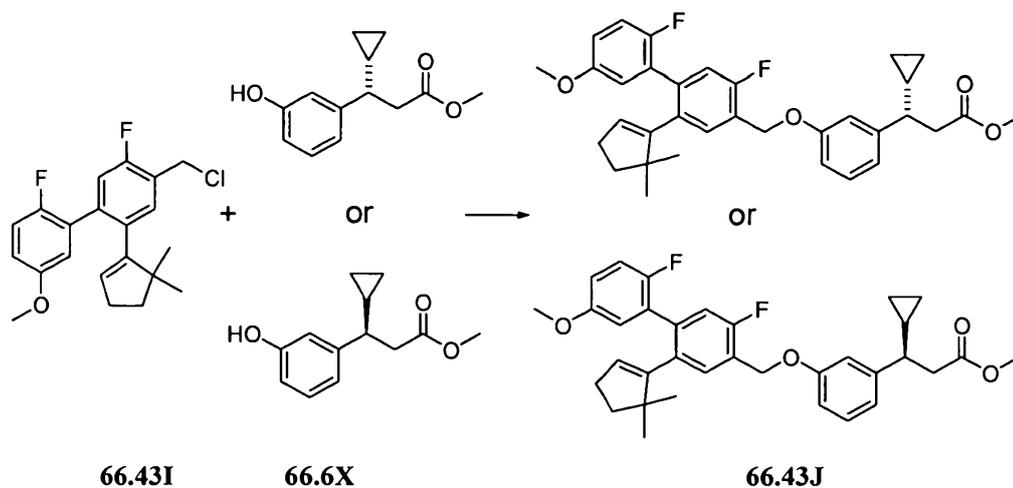


[0748] **(2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (66.43H).** To a cooled solution of **66.43G** (0.92 g, 2.47

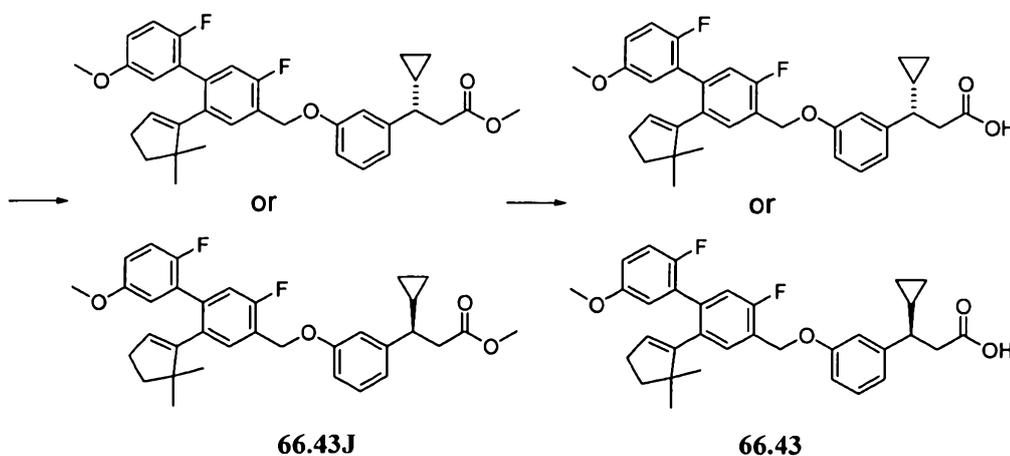
mmol) in dry THF (15 mL) at 0 °C was added LAH (1.0 M in THF)(5.0 mL, 5.0 mmol) dropwise. Upon complete addition, the reaction was maintained at 0°C and was monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction (gas evolution occurred). The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified by flash chromatography (silica gel 60, eluted with 0%-50% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **66.43H** as a colorless oil (0.70 g, 82 % yield). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.30 (1 H, m), 7.05 (1 H, dd, J=10.6, 1.1 Hz), 6.97 (1 H, t, J=8.9 Hz), 6.83 (2 H, m), 5.52 (1 H, td, J=2.4, 0.9 Hz), 4.81 (2 H, s), 3.76 (3 H, s), 2.25 (2 H, td, J=7.1, 2.4 Hz), 1.76 (1 H, br. s.), 1.69(2 H, m), 0.85 (6 H, s).



[0749] **4-(Chloromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl (66.43I)**. To a solution of **66.43H** (0.17 g, 0.48 mmol) in dry DCM (2.0 mL) and dry DMF (0.020 mL) was added thionyl chloride (0.080 mL, 1.1 mmol) dropwise at 0 °C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **66.43I** as a colorless oil (0.16 g, 93% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.29 (1 H, d, J=7.8 Hz), 7.08 (1 H, d, J=10.2 Hz), 6.98 (1 H, t, J=9.0 Hz), 6.85 (2 H, m), 5.56 (1 H, s), 4.69 (2 H, s), 3.77 (3 H, s), 2.27 (2 H, td, J=7.0, 2.7 Hz), 1.68 (2 H, t, J=7.0 Hz), 0.86 (6 H, s).



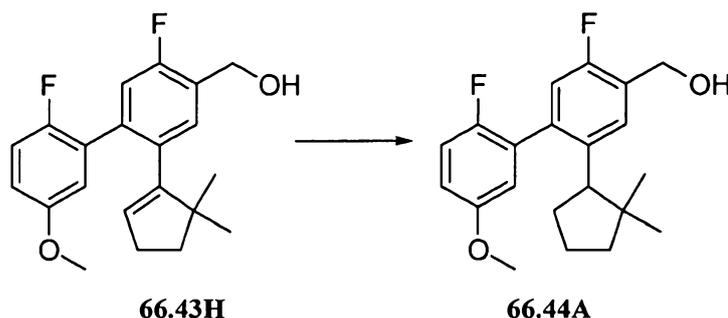
[0750] **Methyl (3S)-3-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.43J).** To a vial containing **66.6X** (23.3 mg, 0.11 mmol) in 1.0 mL dry DMF was added cesium carbonate (42.0 mg, 0.13 mmol). The mixture was stirred at room temperature for 10 minutes and then **66.43I** (42.4 mg, 0.12 mmol) was added. After 22 hours, the reaction was diluted with water and then extracted five times with EtOAc. The combined organic layers were then washed one time with brine and dried over anhydrous magnesium sulfate. The solid was filtered off, and the solvent was concentrated. The residue was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to afford **66.43J** as a colorless oil (50.6 mg, 88% yield). MS ESI (pos.) m/e: 568.9 (M+H₂O)⁺.

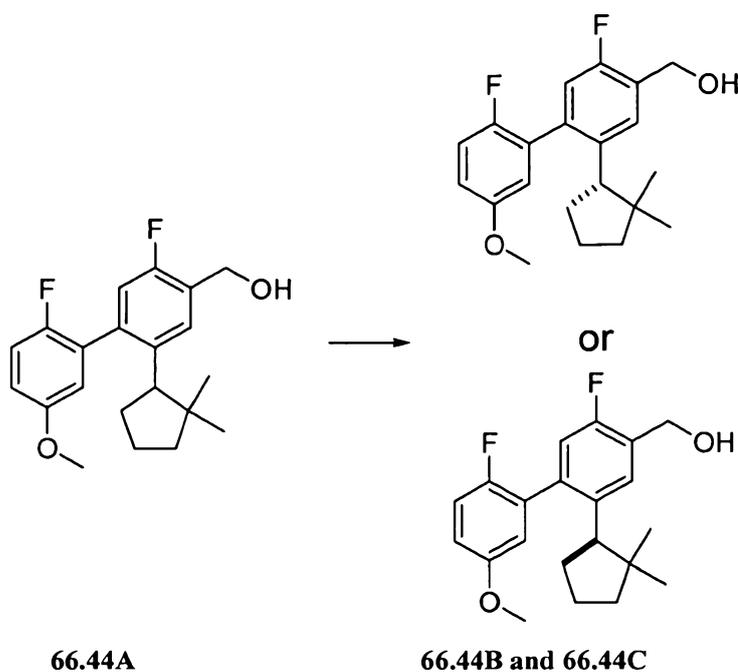


[0751] (3S)-3-Cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.43). A pre-mixed solution of 2M NaOH (0.50 mL, 1.00 mmol), MeOH (1.00 mL), and THF (1.00 mL) was added to a vial containing 66.43J (50.6 mg, 0.0926 mmol). This solution was stirred at room temperature and monitored with TLC and LC-MS. After 24 hours, the mixture was diluted with water and acidified with 1M aqueous HCl solution and then extracted five times with EtOAc. The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel flash chromatography (0-40% EtOAc/hexane) to afford 66.43 as a colorless oil (37.2 mg, 76% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.40 (1 H, d, J=7.4 Hz), 7.30 (1 H, d, J=7.0 Hz), 7.12 (1 H, d, J=10.2 Hz), 7.01 (1 H, t, J=8.8 Hz), 6.96 (3 H, m), 6.88 (2 H, m), 5.55 (1 H, s), 5.20 (2 H, s), 3.80 (3 H, s), 2.83 (2 H, ddd, J=20.0, 15.3, 7.4 Hz), 2.46 (1 H, m), 2.28 (2 H, td, J=6.9, 2.2 Hz), 1.69 (2 H, t, J=7.0 Hz), 1.12 (1 H, m), 0.85 (6 H, s), 0.69 (1 H, m), 0.51 (1 H, m), 0.34 (1 H, dq, J=9.7, 4.8 Hz), 0.20 (1 H, dq, J=9.6, 4.9 Hz). MS ESI (neg.) m/e: 531.0 (M-H)⁺.

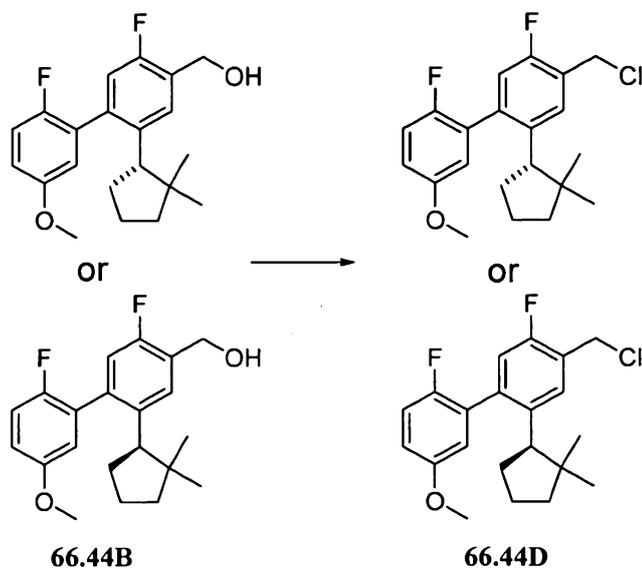
[0752]

Example 66.44

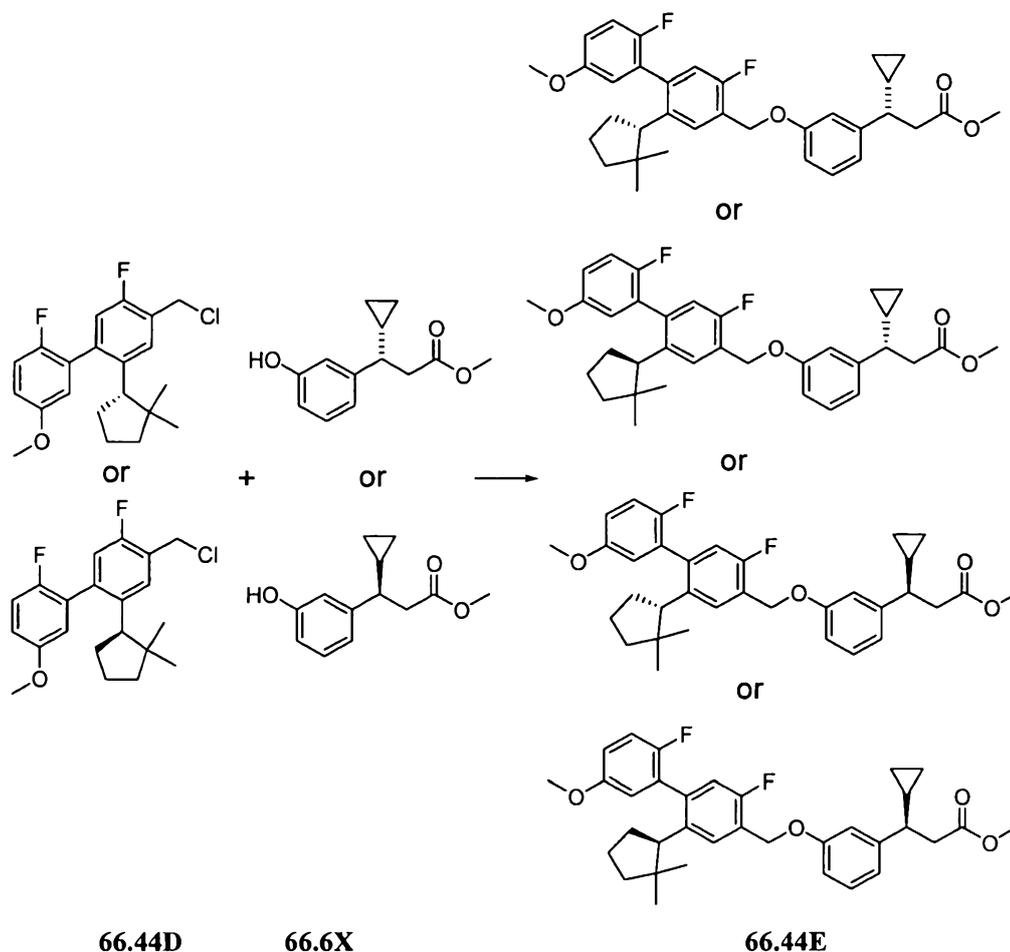




[0753] **(2-(2,2-Dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (66.44A)**. To a dry flask containing **66.43H** (0.70 g, 2.03 mmol) in dry MeOH (5 mL) and EtOAc (3 mL) was added palladium, 10 wt. % on activated carbon (77.2 mg). After purging, the mixture was stirred under an atmosphere of hydrogen at room temperature. After 4.5 hours, the mixture was filtered through Celite. After concentration, the residue was identified as **66.44A** as a mixture of enantiomers and rotamers (0.31 g, 45 % yield). Chiral separation of **66.44A** was accomplished on Chiracel-OJ (2% IPA in hexane) to provide **66.44B** (peak 1) and **66.44C** (peak 2). Both enantiomers were used to synthesize example compounds, and both enantiomers gave active compounds.

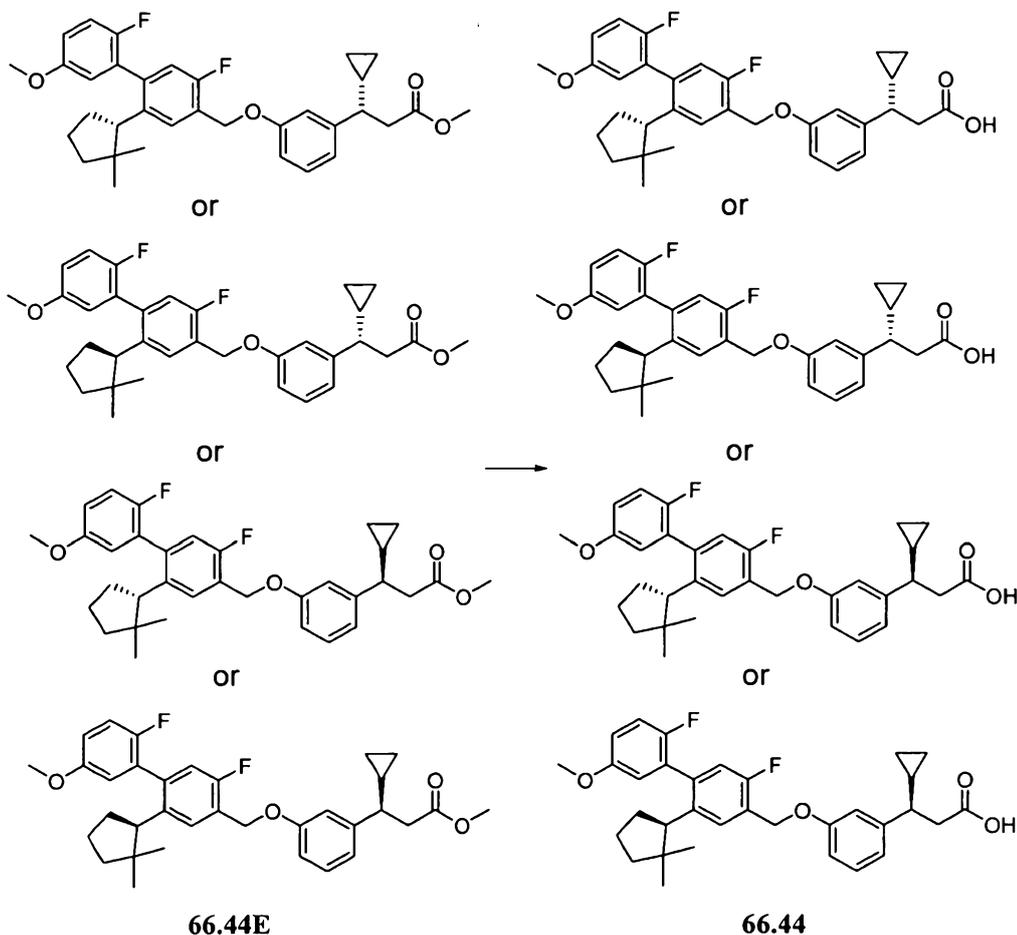


[0754] 4-(Chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl (**66.44D**). To a solution of **66.44B** (0.71 g, 2.05 mmol) in dry DCM (23 mL) and dry DMF (0.18 mL) was added thionyl chloride (0.3 mL, 4.1 mmol) dropwise at 0 °C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to yield **66.44D** as a colorless oil (0.73 g, 97 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.46 (1 H, m), 7.11 (3 H, m), 6.75 (1H, m), 4.78 (2 H, m), 3.80 (3 H, s), 2.91 (1 H, m), 2.20 (2 H, m), 1.87 (2 H, m), 1.59 (1 H, m), 1.43 (1 H, m), 0.77 (3 H, m), 0.64 (3 H, m).



[0755] Methyl (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3S)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.44E). To a vial containing 66.6X (21.0 mg, 0.0953 mmol) in 1.0 mL dry DMF was added cesium carbonate (34.4 mg, 0.106 mmol). The mixture was stirred at room temperature for 10 minutes, and then 66.44D (derived from peak 1 from the chiral separation of 66.44A) (36.6 mg, 0.100 mmol) was added. After 22 hours, the reaction was diluted with water and then extracted five times with EtOAc. The combined organic layers were then washed one time with brine and dried

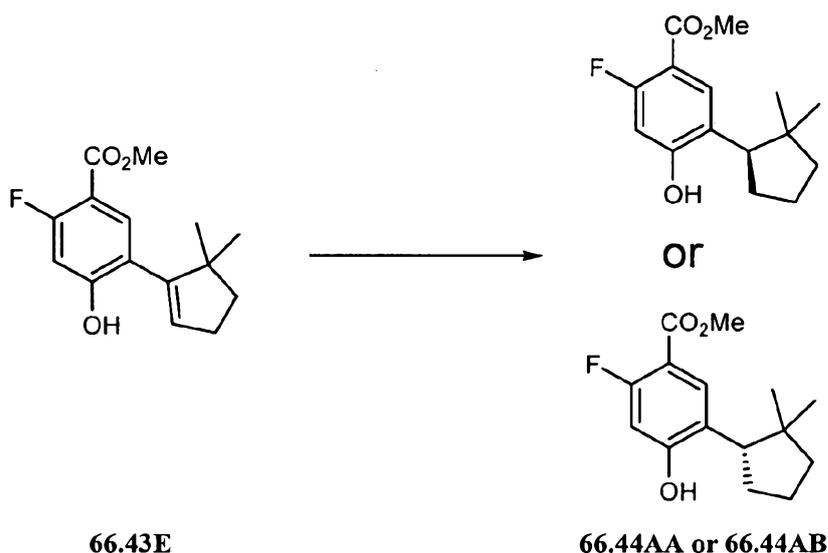
over anhydrous magnesium sulfate. The solid was filtered off, and the solvent was concentrated. The residue was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to afford **66.44E** as a colorless oil (48.8 mg, 93% yield). MS ESI (pos.) m/e : 566.0 ($M+H_2O$)⁺.



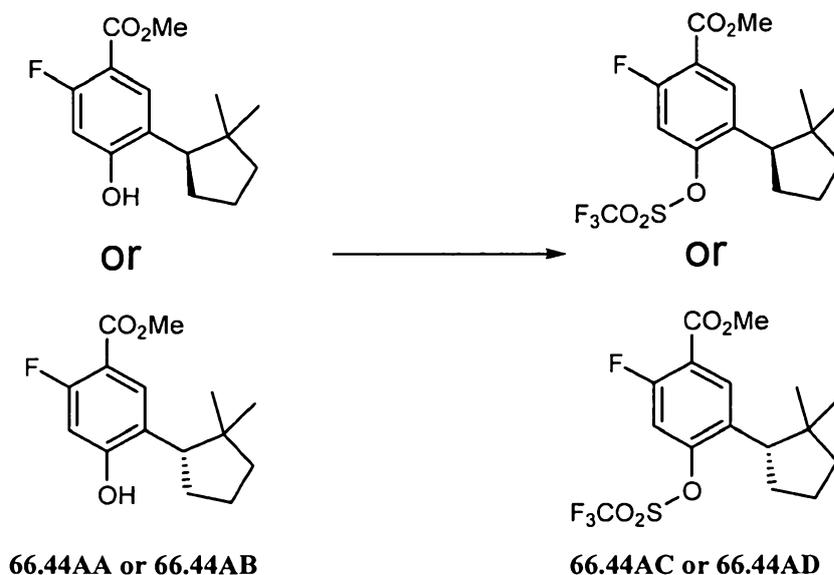
[0756] **(3S)-3-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.44).** A pre-mixed solution of 2M NaOH (0.50 mL, 1.00 mmol), MeOH (1.00 mL), and THF (1.00 mL) was added to a vial

containing **66.44E** (48.8 mg, 0.0889 mmol). The resulting solution was stirred at room temperature and monitored with TLC and LC-MS. After 24 hours, the mixture was diluted with water and acidified with 1M aqueous HCl solution. The resulting mixture was then extracted five times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel flash chromatography (0-30% EtOAc/hexane) to afford **66.44** as a colorless oil (37.4 mg, 79% yield). MS ESI (neg.) m/e : 532.9 (M-H)⁻.

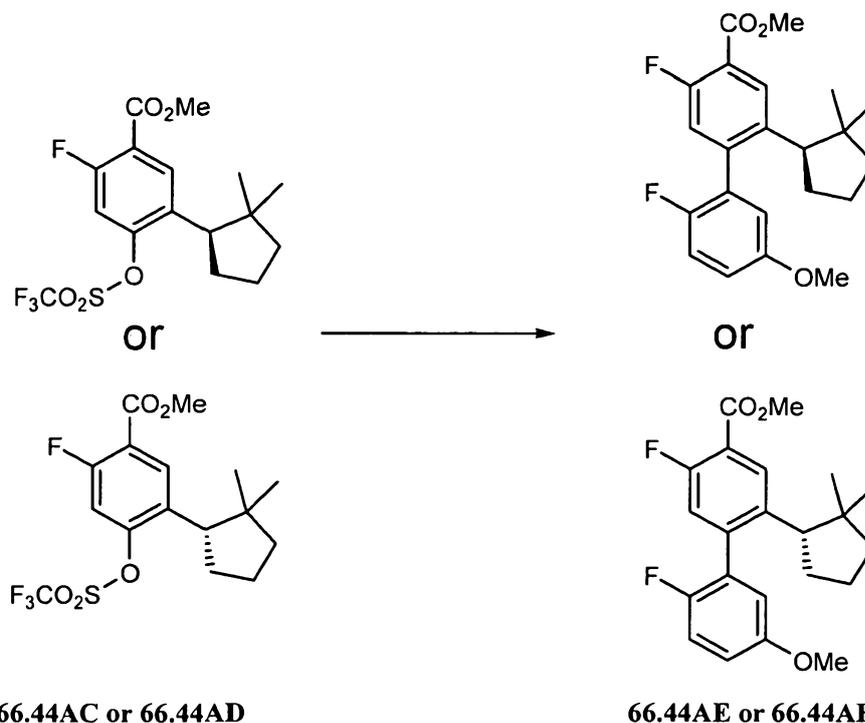
[0757] Asymmetric Synthesis of 66.44B or 66.44C



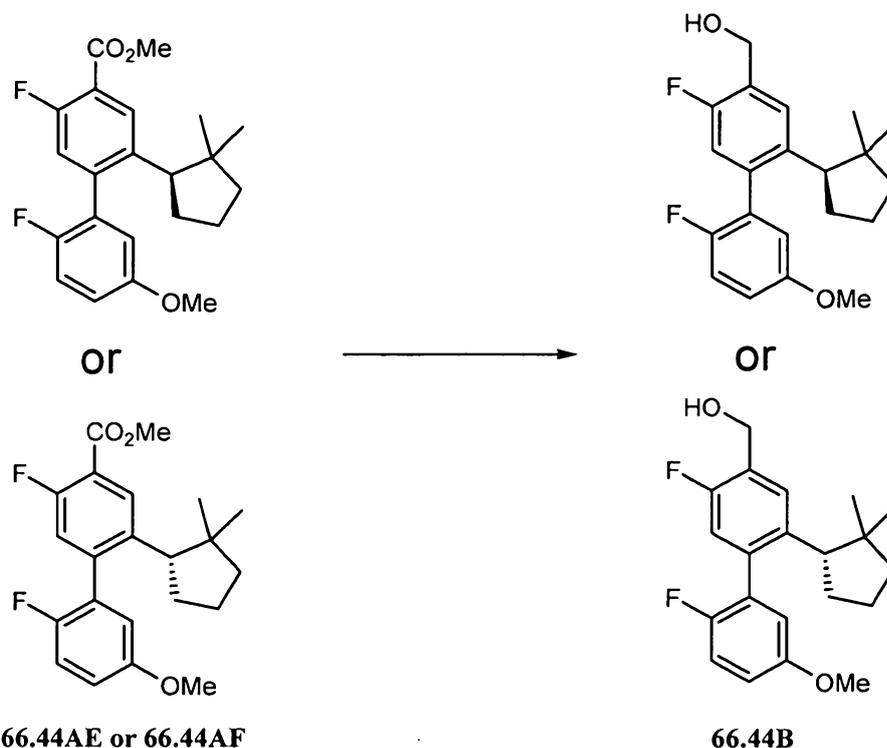
[0758] (R)-Methyl 5-(2,2-dimethylcyclopentyl)-2-fluoro-4-hydroxybenzoate or (S)-methyl 5-(2,2-dimethylcyclopentyl)-2-fluoro-4-hydroxybenzoate (66.44AA or 66.44AB). A mixture of Rh(COD)₂BF₄ (Stern Chemical) 35138-22-8, 36.95 mg, 0.091 mmol) and (R)-1-[(S)-2-(R)-(Ditertbutylphosphino)ferrocenyl]ethyl-bis-(3,5-bistrifluoromethylphenyl)phosphine (Solvias, SL-J210-1, 81.5 mg, 0.100 mmol), was stirred in THF (75 mL) under N₂ for 60 minutes and a dark red solution formed. To the resulting solution was added **66.43E** (8.2g, 45.4 mmol) and TEA (10mol%, 0.63 mL, 4.54 mmol). The resulting solution was filled with H₂ (200 psi) three times and stirred at room temperature under 200 psi H₂ for 2 hours. The resulting mixture was passed through a short plug of silica gel, eluting with 1:1 hexane/EtOAc and then concentrated affording the desired product as a white solid (83% yield (6.8 g), 99.3% ee). The other enantiomer may be obtained as the majority product using the enantiomer of the ferrocenyl compound.



[0759] (R)-Methyl 5-(2,2-dimethylcyclopentyl)-2-fluoro-4-(trifluoromethylsulfonyloxy)benzoate or (S)-methyl 5-(2,2-dimethylcyclopentyl)-2-fluoro-4-(trifluoromethylsulfonyloxy)benzoate (**66.44AC** or **66.44AD**). To a stirred solution of **66.44AA** or **66.44AB** (4.02 g, 15.1 mmol) in dry DCM (50 mL) was added TEA (4.2 mL, 30.2 mmol) and DMAP (0.19 g, 1.52 mmol). After 20 minutes, N-phenyl-bis(trifluoromethanesulfonimide) (5.94 g, 16.6 mmol) was added in portions. Upon complete addition, the solution was stirred at room temperature and monitored with TLC and LC-MS. After 4 hours, the mixture was washed twice with brine, dried over anhydrous magnesium sulfate. After filtration and concentration, the residue was purified with silica gel chromatography (0-10% EtOAc in hexanes) to yield **66.44AC** or **66.44AD** as a colorless oil (5.51, 92%). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.97 (1 H, d, J=7.8 Hz), 7.14 (1 H, d, J=10.0 Hz), 3.96 (3 H, s), 3.13 (1 H, dd, J=10.1, 8.2 Hz), 2.14 (2 H, m), 1.96 (2 H, m), 1.70 (2 H, m), 1.00 (3 H, s), 0.69 (3 H, s).

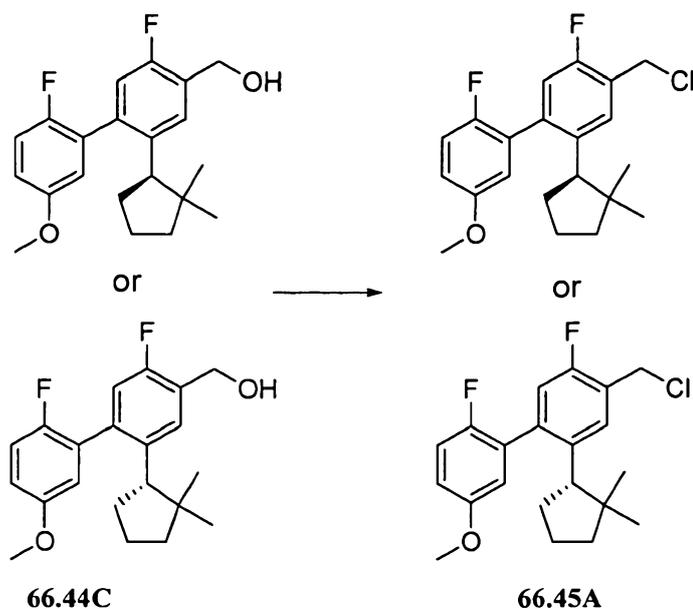


[0760] **Methyl 2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate or methyl 2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.44AE or 66.44AF).** To a stirred solution of **66.44AC or 66.44AD** (5.51 g, 13.8 mmol) in DMF (25 mL) at 23 °C was added 2-fluoro-5-methoxyphenylboronic acid (4.71 g, 27.7 mmol) (commercially available from Aldrich and potassium carbonate (5.74 g, 41.6 mmol) followed by tetrakis(triphenylphosphine)palladium (1.60 g, 1.39 mmol). The mixture was heated to 90 °C. After 3.5 hours, the mixture was cooled to room temperature and then diluted with water. After extracting three times with EtOAc, the mixture was concentrated in vacuo and then purified on silica gel (0%-10% EtOAc/hexane) to yield **66.44AE or 66.44AF** as an oil that solidified (5.11 g, 99%).

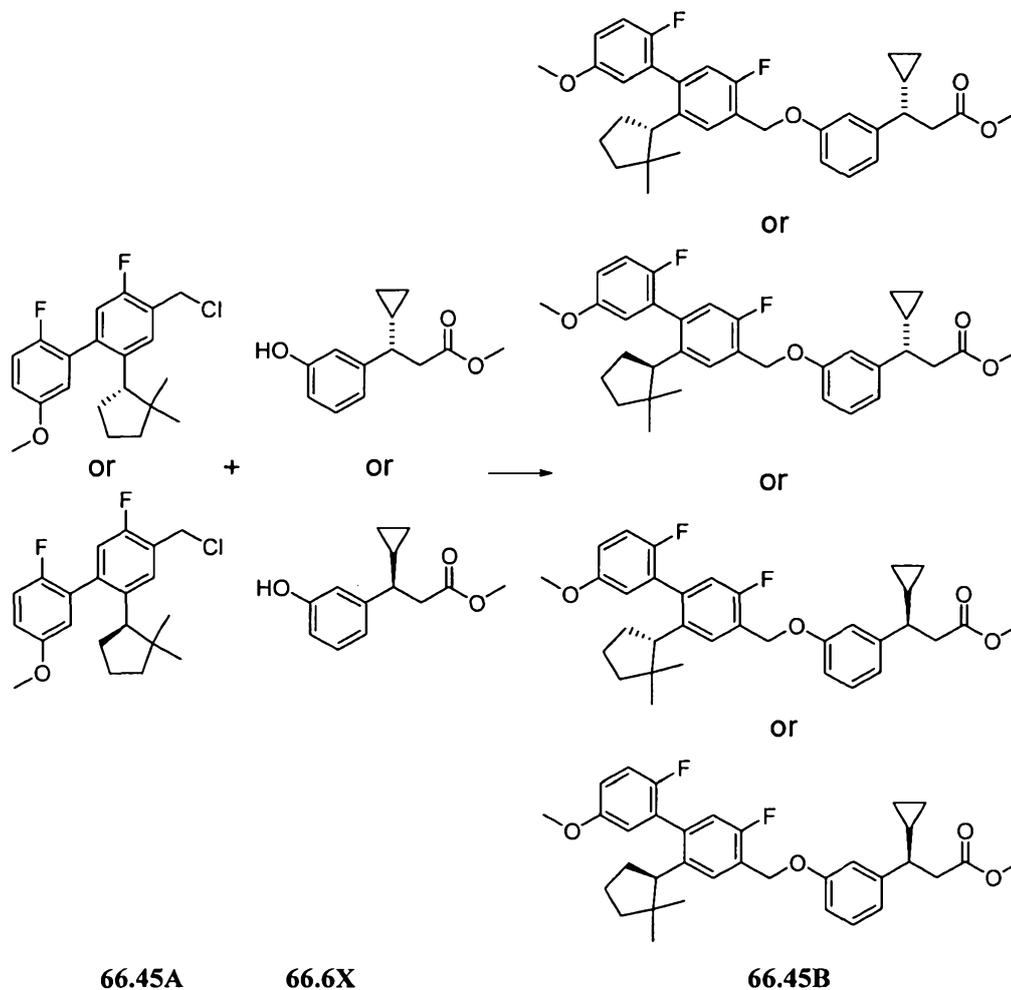


[0761] (2-((1R)-2,2-Dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol or (2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (**66.44B**). To a cooled solution of **66.44AE** or **66.44AF** (5.11 g, 13.6 mmol) in dry THF (40 mL) at 0°C was added LAH, (1.0 M in THF)(27.3 mL, 27.30 mmol) dropwise. Upon complete addition, the reaction was maintained at 0°C and was monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction (gas evolution occurred). The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified by silica gel chromatography (0-25% EtOAc in hexanes) to yield **66.44B** (this enantiomer corresponds to peak one from the chiral separation of **66.44A** on the OJ column) as a colorless oil (3.94 g, 83 %). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.50 (1 H, m), 7.11 (3 H, m), 6.85 (1H, m), 4.81 (2 H, s), 3.80 (3 H, s), 2.92 (1H, m), 2.19 (2 H, m), 1.83 (1 H, m), 1.72 (1 H, m), 1.59 (2 H, m), 1.42 (1 H, m), 0.82 (3 H, m), 0.65 (3 H, m).

[0762] Example 66.45

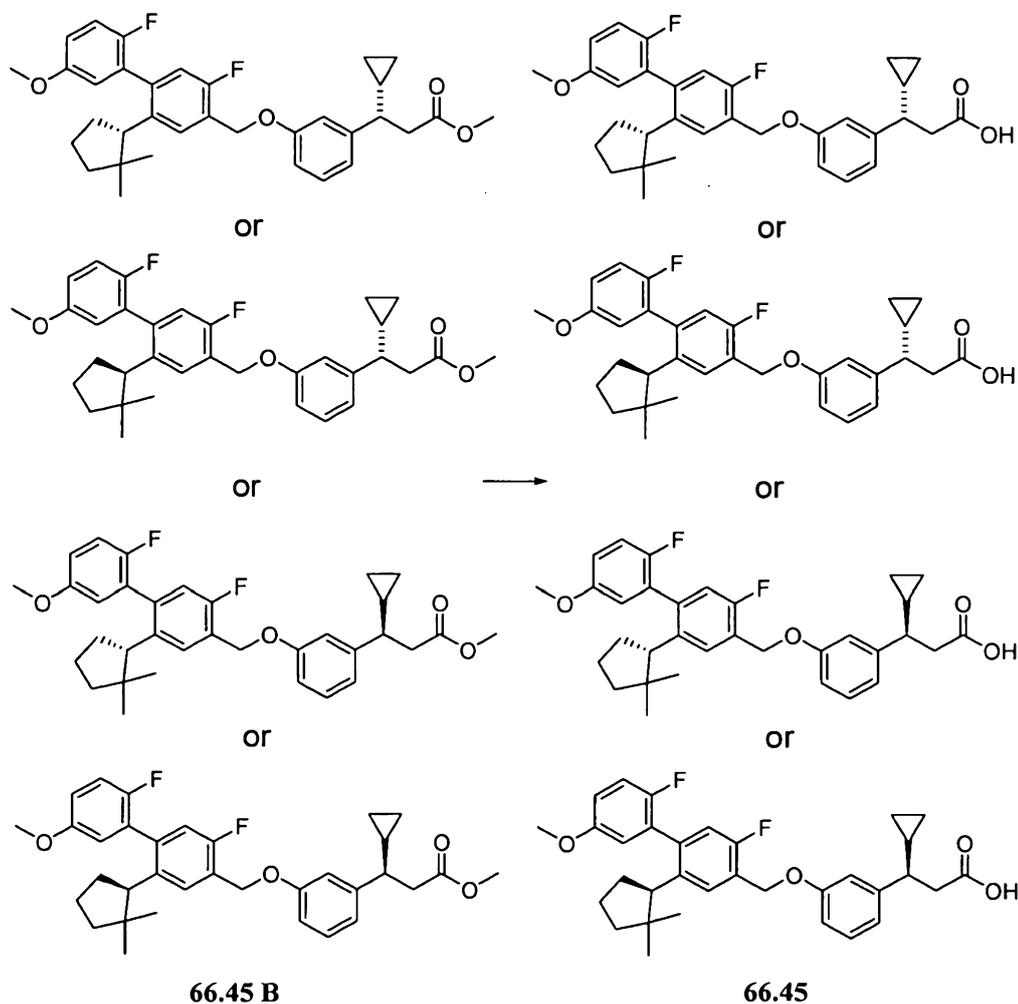


[0763] **4-(Chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl (66.45A).** To a solution of **66.44C** (40.0 mg, 0.12 mmol) in dry DCM (2.0 mL) and dry DMF (0.010 mL) was added thionyl chloride (0.020 mL, 0.27 mmol) at 0°C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **66.45A** as a colorless oil (39.9 mg, 95% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.46 (1 H, m), 7.11 (3 H, m), 6.75 (1H, m), 4.78 (2 H, m), 3.80 (3 H, s), 2.91 (1 H, m), 2.20 (2 H, m), 1.87 (2 H, m), 1.59 (1 H, m), 1.43 (1 H, m), 0.77 (3 H, m), 0.64 (3 H, m).



[0764] Methyl (3S)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.45B). To a vial containing 66.6X (23.1 mg, 0.105 mmol) in 1.0 mL dry DMF was added cesium carbonate (38.7 mg, 0.119 mmol). The mixture was stirred at room temperature for 10 minutes and then 66.45A (39.9 g, 0.109 mmol) was added. After 22 hours, the reaction was diluted with water and then extracted five times with EtOAc. The combined organic layers were then washed one time with brine and dried over anhydrous magnesium sulfate. The solid was filtered off,

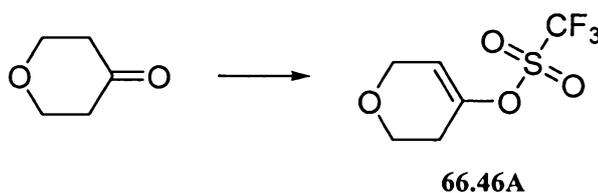
and the solvent was concentrated. The residue was purified by silica gel flash chromatography (0-20% EtOAc/hexane) to afford **66.45B** as a colorless oil (57.5 mg, 96% yield). MS ESI (pos.) m/e: 566.0 (M+H₂O)⁺.



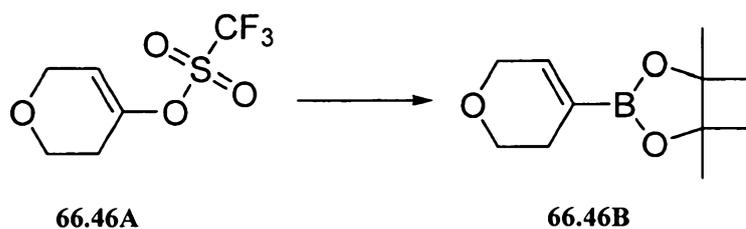
[0765] (3S)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (**66.45**). A pre-mixed solution of 2M NaOH

(0.50 mL, 1.00 mmol), MeOH (1.00 mL), and THF (1.00 mL) was added to a vial containing **66.45B** (55.3 mg, 0.101 mmol). The resulting solution was stirred at room temperature and monitored by TLC and LC-MS. After 24 hours, the mixture was diluted with water and acidified with 1M aqueous HCl solution. The mixture was then extracted five times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel flash chromatography (0-30% EtOAc/hexane) to afford **66.45** as a colorless oil (53.9 mg, 71% yield). MS ESI (neg.) m/e: 532.9 (M-H)⁺.

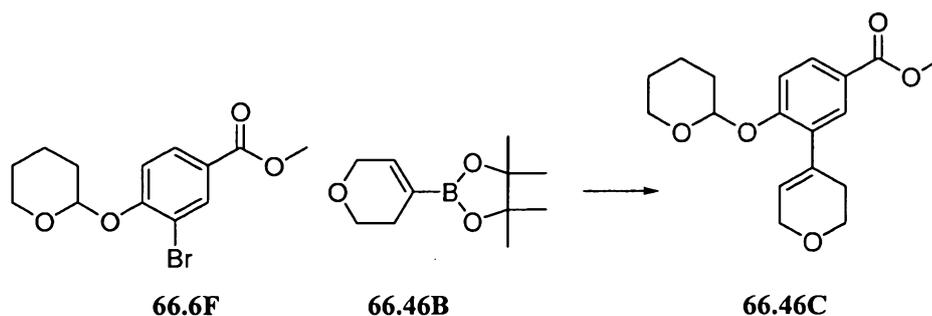
[0766] **Example 66.46**



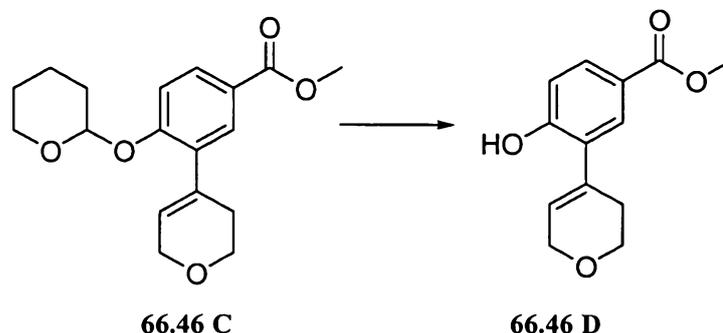
[0767] **3,6-Dihydro-2H-pyran-4-yl trifluoromethanesulfonate (66.46A)**. To a -78 °C solution of tetrahydropyran-4-one (2.0 mL, 21.65 mmol)(commercially available from Aldrich) in dry THF (47.0 mL) was added LDA (2.0 M in heptane/THF/ethylbenzene) (12.5 mL, 25.00 mmol) dropwise under nitrogen. Stirring was continued for 45 minutes at the same temperature to afford a cloudy yellow mixture, to which a solution of N-phenyl-bis(trifluoromethanesulfonimide) (8.5 g, 23.83 mmol) in dry THF (24.00 mL) was added dropwise via syringe. The cooling bath was removed, and the mixture was stirred at room temperature. After 3 hours, the mixture was concentrated and then diluted with water. After extracting three times with hexanes, the combined organic layers were washed brine. After drying over anhydrous magnesium sulfate and subsequent filtration, the solvent was removed under reduced pressure. The residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-5% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to afford **66.46A** as a colorless oil (1.89 g, 38% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 5.82 (1 H, tt, J=2.9, 1.4 Hz), 4.26 (2 H, q, J=2.7 Hz), 3.91 (2 H, m), 2.49 (2 H, m).



[0768] **4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyran (66.46 B).** A mixture of triphenylphosphine (0.21 g, 0.82 mmol), potassium phenolate (1.50 g, 11.38 mmol), bis(pinacolato)diboron (2.06 g, 8.1 mmol), and **66.46A** (1.88 g, 8.1 mmol) in dry toluene (35.00 mL) was degassed by flushing with nitrogen. Dichlorobis(triphenylphosphine)palladium (II) (0.2855 g, 0.4068 mmol) was then added. The mixture was degassed with nitrogen again and then heated to 50°C. After 5 hours, the reaction was cooled to room temperature and then filtered. After concentration, the residue was purified on silica gel using 0-5% EtOAc in hexanes to afford **66.46B** as a colorless oil contaminated with triphenylphosphine oxide (1.40 g, 82% yield). **66.46B** was used without further purification.

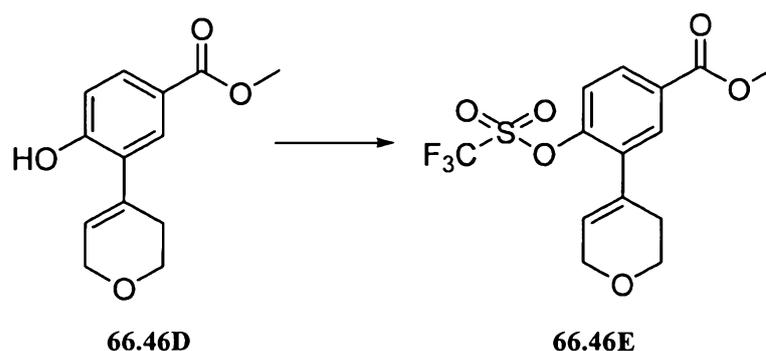


[0769] **Methyl 3-(3,6-dihydro-2H-pyran-4-yl)-4-(tetrahydro-2H-pyran-2-yloxy)benzoate (66.46C).** A stirred mixture of **66.6 F** (1.40 g, 4.45 mmol), ground S-Phos (0.38 g, 0.920 mmol), palladium acetate (0.11 g, 0.475 mmol), **66.46B** (1.40 g, 6.65 mmol), and potassium phosphate tribasic (2.48 g, 11.7 mmol) in DMF (10.0 mL) and water (0.5 mL) was purged three times with argon. The mixture was heated to 75°C and monitored with LC-MS. After 21 hours, the reaction was cooled to room temperature and then diluted with water and extracted three times with EtOAc. The organic layers were combined and washed twice with brine. After drying over anhydrous sodium sulfate and filtration, the organic solvent was removed under reduced pressure. The residue was purified on silica gel using 0-20% EtOAc in hexanes to afford **66.46C** as a colorless oil (0.73 g, 52% yield). MS ESI (pos.) m/e: 340.9 (M+Na)⁺.



[0770] Methyl 3-(3,6-dihydro-2H-pyran-4-yl)-4-hydroxybenzoate (66.46D).

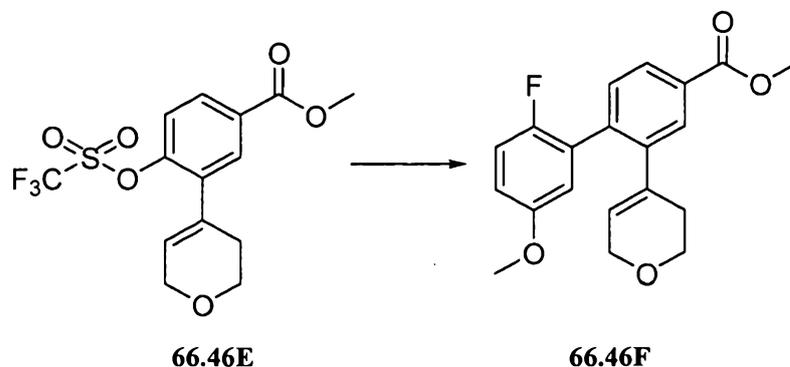
To a stirred mixture of **66.46C** (0.73 g, 2.30 mmol) in MeOH (10 mL) was added PPTS (58.8 mg, 0.234 mmol). The mixture was heated to 45°C and monitored with TLC and LCMS. After 19 hours, the organic solvent was removed under reduced pressure and the residue was purified on silica gel (0-25% EtOAc in hexanes) to afford **66.46D** (361 mg, 67% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.87 (2 H, td, J=8.7, 2.2 Hz), 6.95 (1 H, d, J=8.6 Hz), 6.00 (1 H, m), 5.94 (1 H, s), 4.34 (2 H, q, J=2.7 Hz), 3.97 (2 H, t, J=5.5 Hz), 3.89 (3 H, s), 2.47 (2 H, ddd, J=9.8, 5.5, 2.7 Hz).



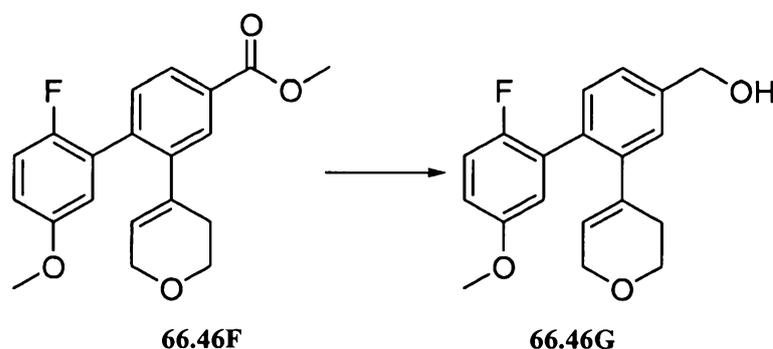
[0771] Methyl 3-(3,6-dihydro-2H-pyran-4-yl)-4-

(((trifluoromethyl)sulfonyl)oxy)benzoate (66.46E). To a stirred solution of **66.46D** (361 mg, 1.54 mmol) in dry DCM (10 mL) was added TEA (0.42 mL, 3.02 mmol) and 4-dimethylaminopyridine (19.0 mg, 0.156 mmol). After about 20 minutes, N-phenyl-bis(trifluoromethanesulfonimide) (661.2 mg, 1.85 mmol) was added in portions. Upon complete addition, the solution was stirred at room temperature and monitored with TLC and LC-MS. After 3 hours, the reaction was diluted with brine and extracted three times with DCM. After drying over anhydrous magnesium sulfate and filtration, the organic solvent was removed under reduced pressure, and the residue was purified on silica gel

(0-50% EtOAc in hexanes) to afford **66.46E** (555 mg, 98% yield). MS ESI (pos.) m/e: 383.8 (M+H₂O)⁺.

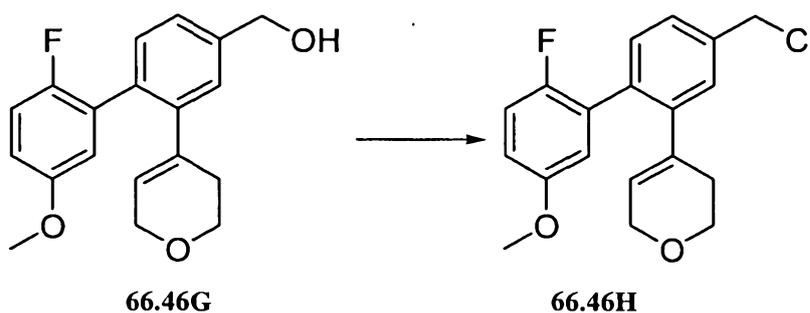


[0772] **Methyl 2-(3,6-dihydro-2H-pyran-4-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.46F)**. To a stirred solution of **66.46E** (555 mg, 1.52 mmol) in DMF (10 mL) at 23 °C was added 2-fluoro-5-methoxyphenylboronic acid (512.3 mg, 3.0 mmol) (commercially available from Aldrich) and potassium carbonate (630.1 mg, 4.56 mmol) followed by tetrakis(triphenylphosphine)palladium(0) (176.8 mg, 0.15 mmol). The mixture was heated to 90 °C. After 18 hours, LCMS showed the reaction was complete. The mixture was cooled to room temperature and diluted with water. After extracting three times with EtOAc, the mixture was concentrated in vacuo, and the residue was purified on silica gel (0-50% EtOAc in hexanes) to afford **66.46F** (452.7 mg, 87% yield). MS ESI (pos.) m/e: 343.0 (M+H)⁺.

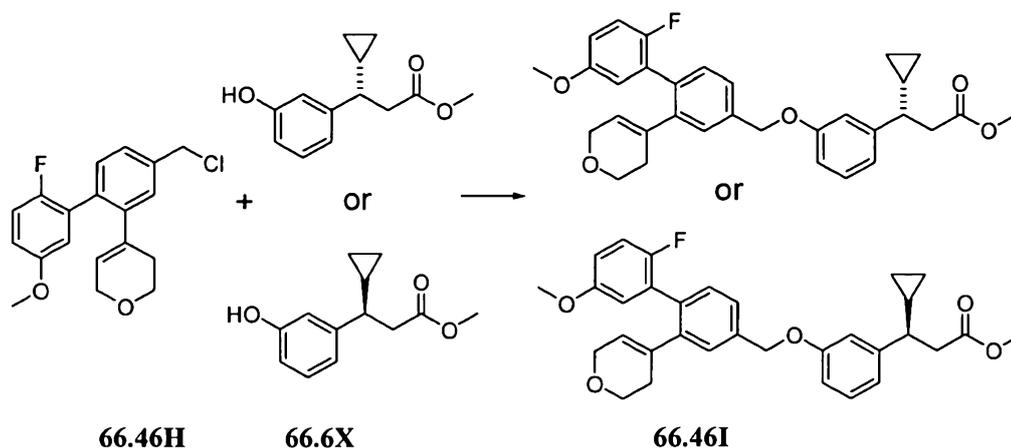


[0773] **(2-(3,6-Dihydro-2H-pyran-4-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (66.46G)**. To a cooled solution of **66.46F** (452.7 mg, 1.3 mmol) in dry THF (10 mL) at 0 °C was added LAH (1.0 M in THF) (2.7 mL, 2.7 mmol) dropwise. Upon complete addition, the reaction was maintained at 0 °C and was

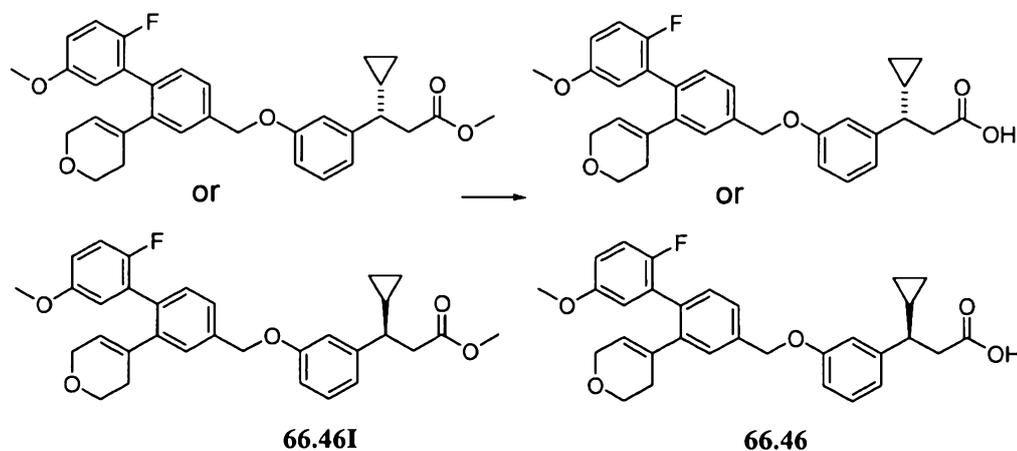
monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction. The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified by flash chromatography (silica gel 60, eluted with 0%-50% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **66.46G** as a colorless oil (330.4 mg, 80%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.33 (3 H, m), 7.03 (1 H, m), 6.84 (2 H, m), 5.51 (1 H, s), 4.69 (2 H, s), 4.08 (2 H, q, J=2.5 Hz), 3.77 (3 H, s), 3.67 (2 H, t, J=5.3 Hz), 3.00 (1 H, s), 2.13 (2 H, m).



[0774] **4-(4-(Chloromethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-3,6-dihydro-2H-pyran (66.46H)**. To a solution of **66.46G** (39.3 mg, 0.13 mmol) in dry DCM (1.0 mL) and dry DMF (0.010 mL) was added thionyl chloride (0.020 mL, 0.27 mmol) at 0°C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **66.46H** (39.5 mg, 95% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.39 (3 H, m), 7.02 (1 H, t, J=8.8 Hz), 6.85 (2 H, m), 5.57 (1 H, s), 4.64 (2 H, s), 4.13 (2 H, q, J=2.7 Hz), 3.80 (3 H, s), 3.70 (2 H, t, J=5.3 Hz), 2.14 (2 H, dd, J=4.5, 2.5 Hz).

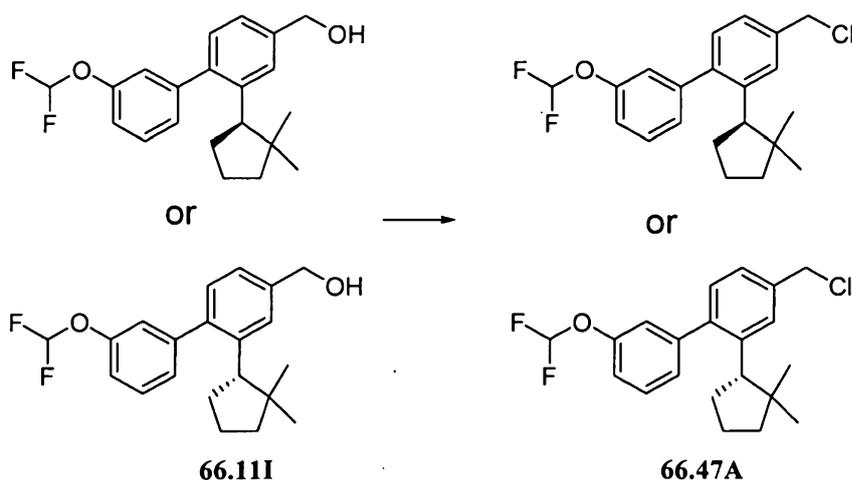


[0775] **Methyl (3S)-3-cyclopropyl-3-(3-(((2-(3,6-dihydro-2H-pyran-4-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2-(3,6-dihydro-2H-pyran-4-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.46I).** To a vial containing **66.6X** (21.5 mg, 0.0976 mmol) in 1.0 mL dry DMF was added cesium carbonate (31.8 mg, 0.0976 mmol). The mixture was stirred at room temperature for 10 minutes and then **66.46H** (39.5 g, 0.119 mmol) was added. After 22 hours, the reaction was diluted with water and then extracted five times with EtOAc. The combined organic layers were washed one time with brine and dried over anhydrous magnesium sulfate. The solid was filtered away, and the solvent was concentrated. The residue was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to afford **66.46I** as a colorless oil (38.9 mg, 77% yield). MS ESI (pos.) m/e: 534.0 (M+H₂O)⁺.



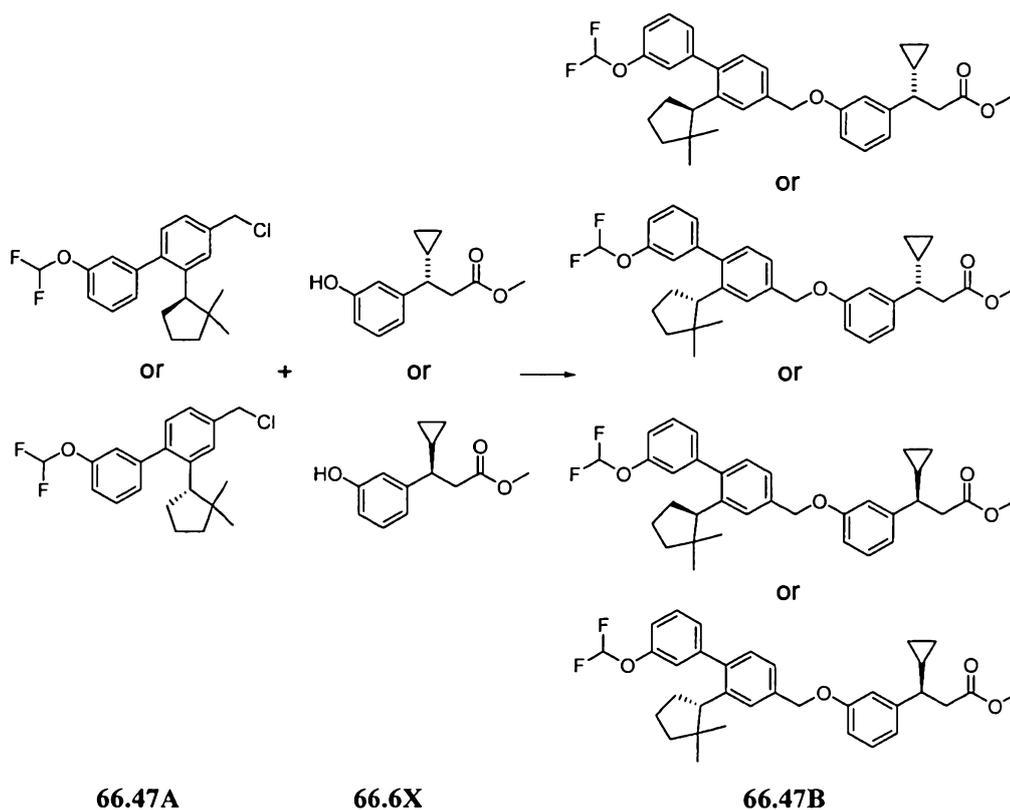
[0776] (3S)-3-Cyclopropyl-3-(3-(((2-(3,6-dihydro-2H-pyran-4-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-(3,6-dihydro-2H-pyran-4-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.46). A pre-mixed solution of 2M NaOH (0.5 mL, 1.00 mmol), MeOH (1.0 mL), and THF (1.0 mL) was added to a vial containing 66.46I (38.9 mg, 0.0753 mmol). The mixture was stirred at room temperature and monitored with TLC and LC-MS. After 24 hours, the mixture was diluted with water and acidified with 1M aqueous HCl and then was extracted five times with EtOAc. The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel flash chromatography (0-40% EtOAc/hexane) to afford 66.46 as a colorless oil (30.2 mg, 80% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.44 (3 H, m), 7.26 (1 H, t, J=7.8 Hz), 7.06 (1 H, m), 6.92 (5 H, m), 5.56 (1 H, s), 5.10 (2 H, s), 4.16 (2 H, m), 3.80 (3 H, s), 3.71 (2 H, t, J=5.3 Hz), 2.79 (2 H, ddd, J=20.0, 15.3, 7.4 Hz), 2.42 (1 H, m), 2.16 (2 H, d, J=2.0 Hz), 1.08 (1 H, m, J=17.7, 7.9, 5.1, 4.9 Hz), 0.64 (1 H, m), 0.44 (1 H, tt, J=8.8, 4.7 Hz), 0.34 (1 H, m), 0.21 (1 H, m). MS ESI (neg.) m/e: 501.0 (M-H)⁺.

[0777] **Example 66.47**



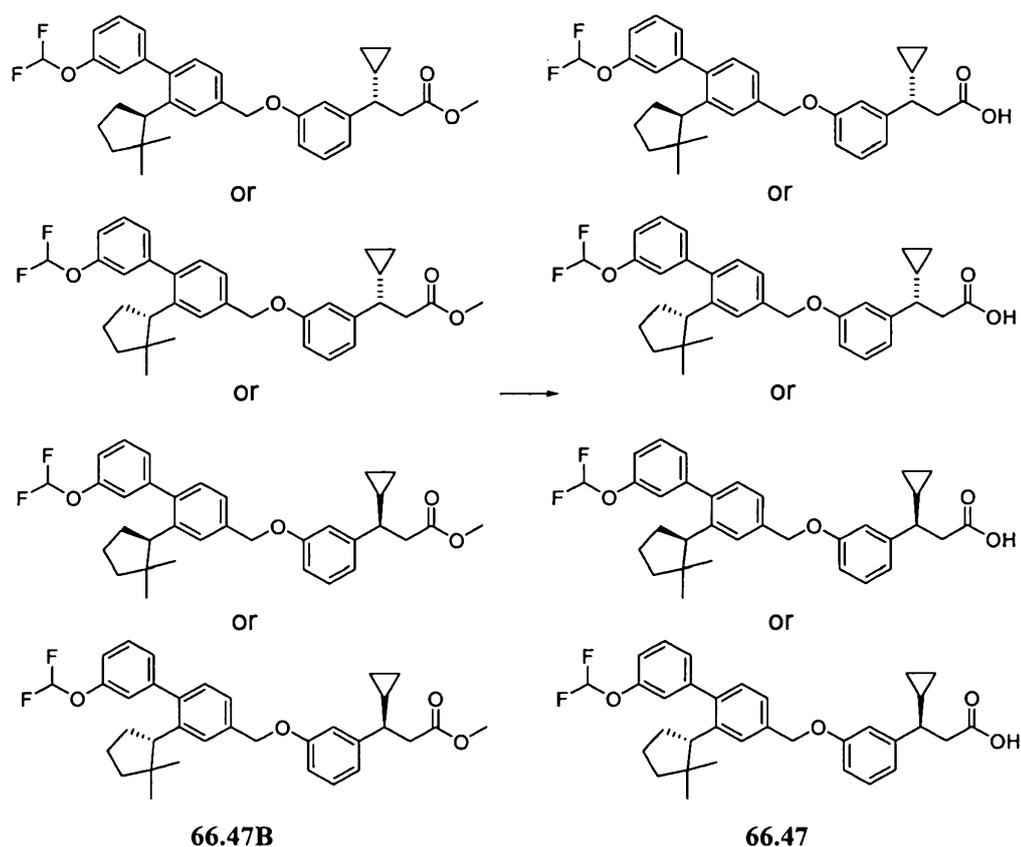
[0778] 4-(Chloromethyl)-3'-((difluoromethyl)oxy)-2-((1R)-2,2-dimethylcyclopentyl)-1,1'-biphenyl or (chloromethyl)-3'-((difluoromethyl)oxy)-2-((1S)-2,2-dimethylcyclopentyl)-1,1'-biphenyl (66.47A). To a solution of 66.11I (110.3 mg, 0.318 mmol) in dry DCM (4.0 mL) and dry DMF (0.03 mL) was added thionyl chloride (0.06 mL, 0.823 mmol) at 0 °C. The resulting solution was warmed to room

temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **66.47A** as a colorless oil (106.1 mg, 91% yield). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 7.42 (2 H, m), 7.25 (1 H, d, $J=2.0$ Hz), 7.20 (1 H, m), 7.11 (2 H, dd, $J=7.8, 2.0$ Hz), 7.03 (1 H, s), 6.54 (1H, t, $J=74$ Hz), 4.71 (2 H, m), 3.04 (1 H, dd, $J=10.4, 8.4$ Hz), 2.14 (2 H, m), 1.88 (1 H, m), 1.74 (1 H, m), 1.54 (2 H, ddd, $J=12.6, 8.1, 4.7$ Hz), 1.41 (1 H, m), 0.73 (3 H, s), 0.56 (3 H, s).



[0779] **Methyl (3S)-3-cyclopropyl-3-(3-(((3'-((difluoromethyl)oxy)-2-((1R)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3S)-3-cyclopropyl-3-(3-(((3'-((difluoromethyl)oxy)-2-((1S)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((3'-((difluoromethyl)oxy)-2-((1R)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((3'-((difluoromethyl)oxy)-2-((1S)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.47B).** To a vial containing

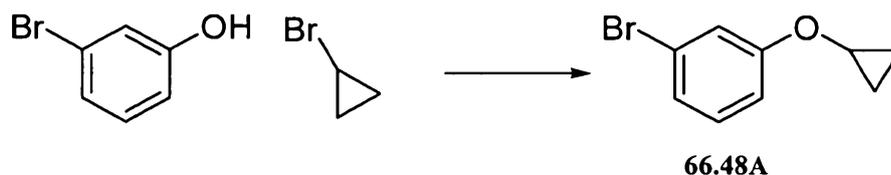
66.6X (16.4 mg, 0.0745 mmol) in 1.0 mL dry DMF was added cesium carbonate (30.1 mg, 0.0924 mmol). The mixture was stirred at room temperature for 10 minutes and then **66.47A** (30.2 mg, 0.0828 mmol) was added. After 22 hours, the reaction was diluted with water and then it was extracted five times with EtOAc. The combined organic layers were then washed one time with brine and dried over anhydrous magnesium sulfate. The solid was filtered off, and the solvent was concentrated. The residue was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to afford **66.47B** as a colorless oil (37.3 mg, 91% yield). MS ESI (pos.) m/e: 566.0 (M+H₂O)⁺.



[0780] (3S)-3-Cyclopropyl-3-(3-(((3'-((difluoromethyl)oxy)-2-((1R)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((3'-((difluoromethyl)oxy)-2-((1S)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((3'-((difluoromethyl)oxy)-2-((1R)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((3'-((difluoromethyl)oxy)-2-((1S)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-

yl)methyl)oxy)phenyl)propanoic acid (66.47). A pre-mixed solution of 2M NaOH (0.30 mL), THF (0.50 mL), and MeOH (0.50 mL) was added to a vial containing 66.47B (37.3 mg, 0.068 mmol). The resulting solution was stirred at room temperature and monitored with TLC and LC-MS. After 24 hours, the mixture was diluted with water and acidified with 1M aqueous HCl solution. The mixture was then extracted five times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel flash chromatography (0-40% EtOAc/hexane) to afford 66.47 as a colorless oil (25.8 mg, 71% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.45 (2 H, m), 7.31 (1 H, dd, J=7.8, 2.0 Hz), 7.28 (3 H, m), 7.14 (2 H, m), 7.04 (1 H, d, J=1.6 Hz), 6.92 (3 H, m), 6.54 (1H, t, J= 78 Hz), 5.10 (2 H, s), 3.05 (1 H, dd, J=10.4, 8.4 Hz), 2.87 (2 H, m), 2.44 (1 H, m), 2.13 (2 H, m), 1.87 (1 H, m), 1.72 (1 H, m), 1.52 (1 H, ddd, J=12.7, 8.2, 4.9 Hz), 1.41 (1 H, m), 1.10 (1 H, m), 0.74 (3 H, m), 0.65 (4 H, m), 0.49 (1 H, m), 0.30 (1 H, dq, J=9.6, 4.8 Hz), 0.22 (1 H, m). MS ESI (neg.) m/e: 532.9 (M-H)⁺.

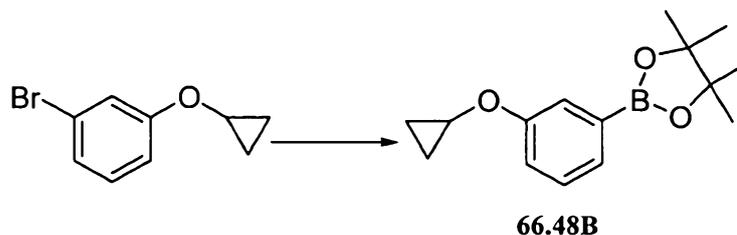
[0781]

Example 66.48

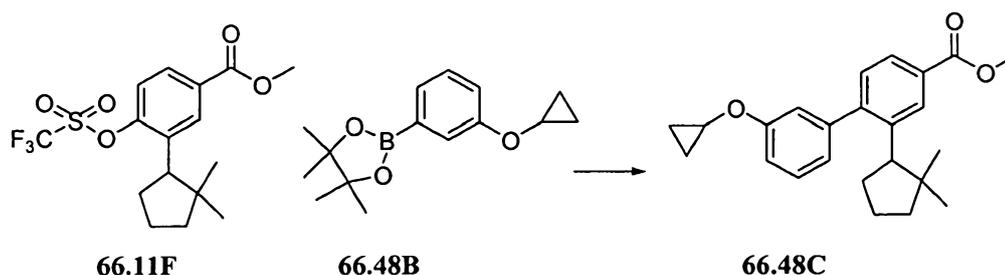
[0782]

3-Bromophenyl cyclopropyl ether (66.48 A).

To a solution of 3-bromophenol (0.57 g, 3.29 mmol)(commercially available from Aldrich) in dry DMF (5.0 mL) was added cyclopropyl bromide (0.53 mL, 6.62 mmol)(commercially available from Aldrich), sodium iodide (50.1 mg, 0.334 mmol), and cesium carbonate (3.2 g, 9.86 mmol). The reaction mixture was heated in a pressure tube to 150°C. After 19 hours, the reaction was cooled to room temperature then diluted with EtOAc, washed with water, and extracted three times with EtOAc. The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford 66.48A as a colorless oil (144 mg, 21% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.29 (1 H, m), 7.19 (2 H, m), 6.99 (1 H, d, J=7.8 Hz), 3.74 (1 H, ddd, J=8.9, 5.8, 3.3 Hz), 0.81 (4 H, ddd, J=11.2, 9.0, 8.8 Hz).

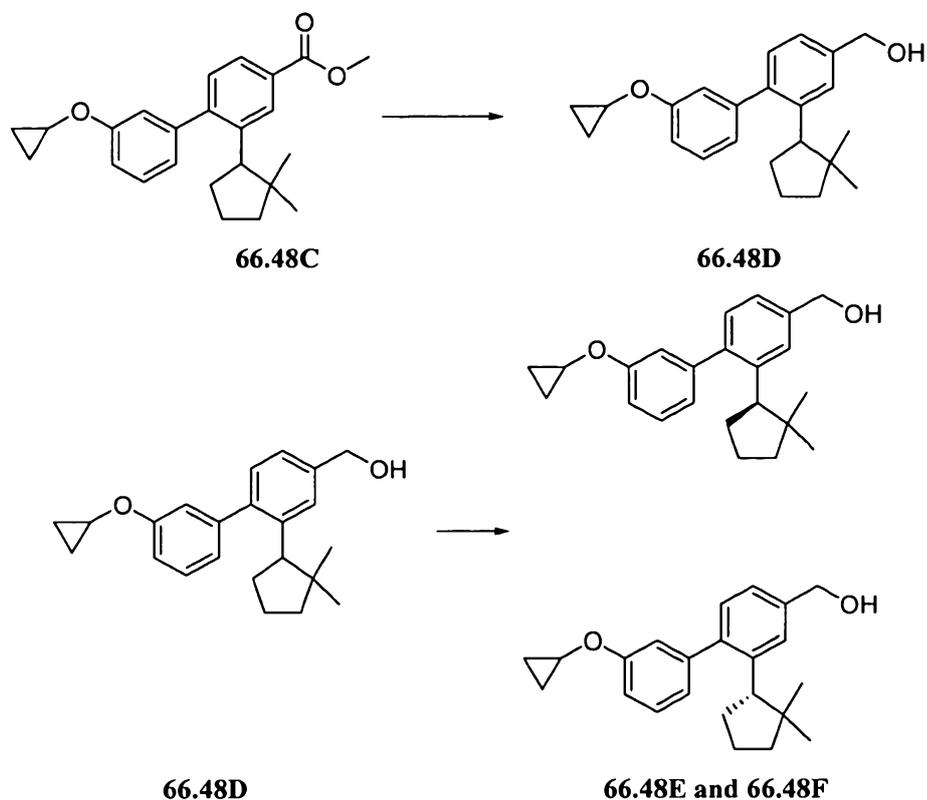


[0783] 2-(3-(Cyclopropyloxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (66.48B). A stirred mixture of **66.48A** (0.144 g, 0.676 mmol), bis(pinacolato)diboron (0.189 g, 0.745 mmol), potassium acetate (0.2007 g, 2.04 mmol), and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) DCM adduct (25.3 mg, 0.0346 mmol) in dry 1,4-dioxane (3.0 mL) was purged three times with argon and placed under vacuum three times. The mixture was heated to 100°C, and monitored with LC-MS and TLC. After 21 hours, the reaction was cooled to room temperature and filtered through Celite. The organic solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to afford **66.48B** as a colorless oil (72 mg, 41% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.51 (1 H, d, J=2.7 Hz), 7.44 (1 H, d, J=7.0 Hz), 7.34 (1 H, m), 7.14 (1 H, dd, J=7.6, 2.2 Hz), 3.80 (1 H, ddd, J=8.8, 5.9, 3.3 Hz), 1.36 (12 H, s), 0.82 (4 H, m).

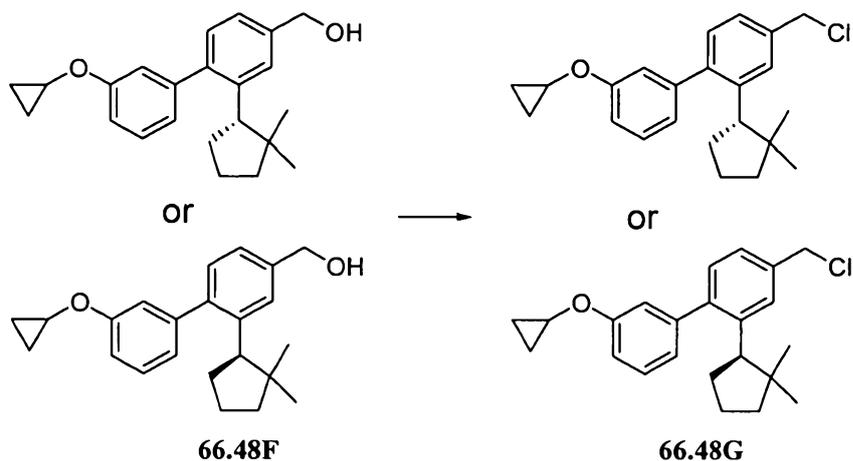


[0784] Methyl 3'-(cyclopropyloxy)-2-(2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-carboxylate (66.48C.) To a stirred solution of **66.11F** (438.2 mg, 1.15 mmol) in dry DMF (5.0 mL) at 23°C was added potassium carbonate (480.3 mg, 3.47 mmol) followed by tetrakis(triphenylphosphine)palladium (140.2 mg, 0.121 mmol). The mixture was purged three times with argon and placed under vacuum three times. Before heating, **66.48B** (523.1 mg, 2.01 mmol) was added via syringe and then the mixture was heated to 90°C. After 19 hours, LCMS showed reaction was complete. The mixture was cooled to room temperature and then diluted with water. After extracting three times with EtOAc, the mixture was concentrated in vacuo and then purified on silica gel (0%-10%

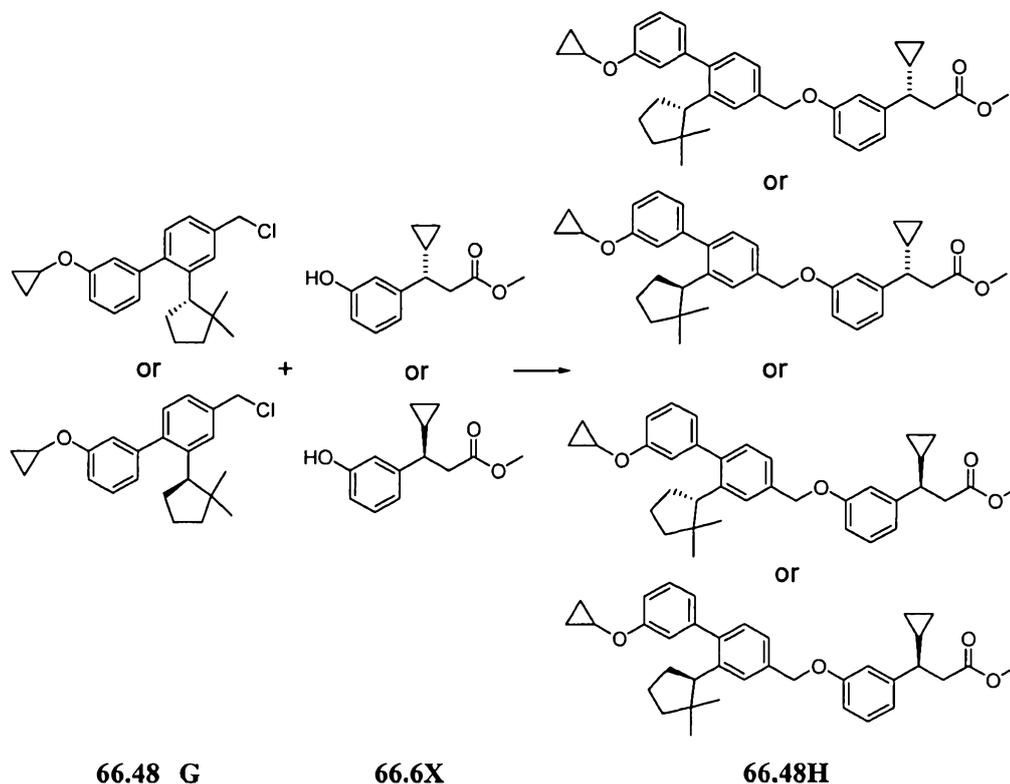
EtOAc/hexane) to afford **66.48C** as a colorless oil that was used without further purification (411.5 mg, 98% yield). MS ESI (pos.) m/e: 365.0 (M+H)⁺.



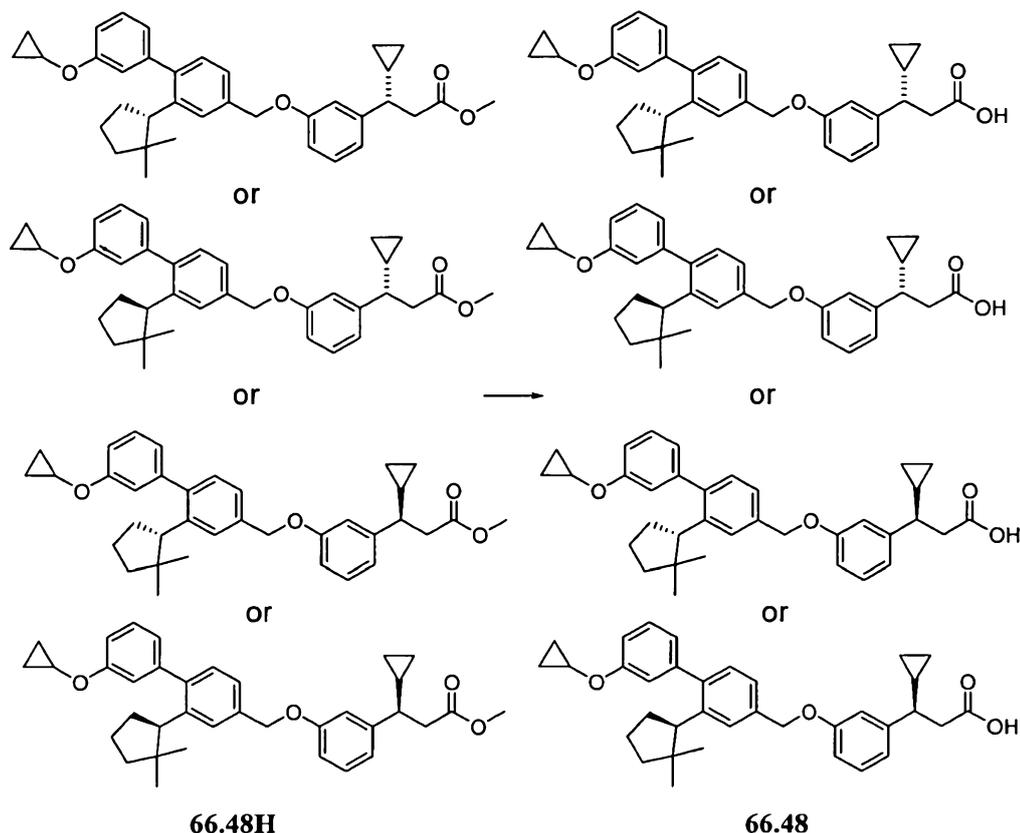
[0785] (3'-(Cyclopropoxy)-2-(2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methanol (**66.48D**). To a cooled solution of **66.48C** (0.4115 g, 1.129 mmol) in dry THF (10 mL) at 0 °C was added LAH (1.0M in THF)(2.30 mL, 2.3 mmol) dropwise. Upon complete addition, the reaction was maintained at 0 °C and was monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction. The resulting mixture was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified by flash chromatography (SiO₂ gel 60, eluted with 0%-50% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to a colorless oil as **66.48D** (317.1 mg, 83% yield). MS ESI (pos.) m/e: 319.0 (M-H₂O)⁺. Chiral separation of **66.48D** was accomplished on Chiracel-OD (3% IPA in hexane) to provide **66.48E** (peak 1) and **66.48F** (peak 2). Both enantiomers were used to synthesize example compounds, and both enantiomers gave active compounds.



[0786] 4-(Chloromethyl)-3'-(cyclopropyloxy)-2-((1S)-2,2-dimethylcyclopentyl)-1,1'-biphenyl or 4-(chloromethyl)-3'-(cyclopropyloxy)-2-((1R)-2,2-dimethylcyclopentyl)-1,1'-biphenyl (**66.48G**). To a solution of **66.48F** (0.1335 g, 0.397 mmol) in dry DCM (4 mL) and dry DMF (0.03 mL) was added thionyl chloride (0.07 mL, 0.96 mmol) at 0°C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **66.48G** as a colorless oil (118.3 mg, 84% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.39 (1 H, d, J=1.6 Hz), 7.34 (1 H, d, J=1.6 Hz), 3.78 (1 H, m), 3.15 (1 H, dd, J=10.4, 3 H, m), 7.01 (1 H, dd, J=7.8, 3.1 Hz), 6.98 (1 H, m), 6.85 (1 H, d, J=7.4 Hz), 4.69 (2 H, m, 8.4 Hz), 2.13 (2 H, m), 1.88 (1 H, m), 1.72 (1 H, m), 1.59 (1 H, m), 1.41 (1 H, m), 0.82 (6 H, m), 0.58 (3 H, s).



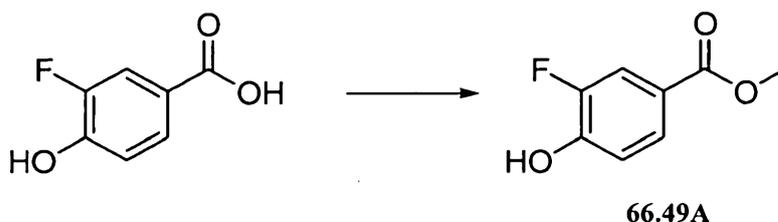
[0787] Methyl (3S)-3-cyclopropyl-3-(3-(((3'-(cyclopropyloxy)-2-((1S)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3S)-3-cyclopropyl-3-(3-(((3'-(cyclopropyloxy)-2-((1R)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((3'-(cyclopropyloxy)-2-((1S)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((3'-(cyclopropyloxy)-2-((1R)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.48H). To a vial containing 66.6X (0.0202 g, 0.0917 mmol) in 1.0 mL dry DMF was added cesium carbonate (0.0389 g, 0.119 mmol). The mixture was stirred at room temperature for 10 minutes and then 66.48G (0.0374 g, 0.105 mmol) was added. After 22 hours, the reaction was diluted with water and then was extracted five times with EtOAc. The combined organic layers were then washed one time with brine and dried over anhydrous magnesium sulfate. The solid was filtered off, and the solvent was concentrated. The residue was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to afford 66.48H as a colorless oil (21.8 mg, 44% yield).



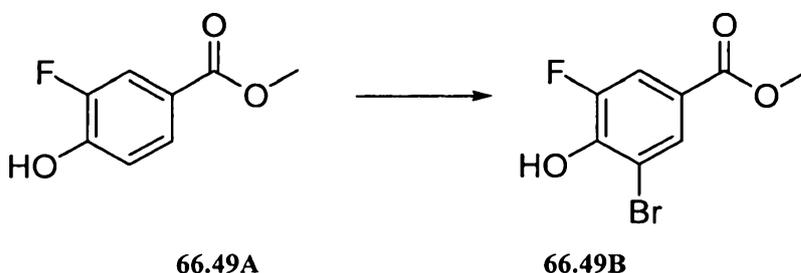
[0788] (3S)-3-Cyclopropyl-3-(3-(((3'-(cyclopropyloxy)-2-((1S)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((3'-(cyclopropyloxy)-2-((1R)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((3'-(cyclopropyloxy)-2-((1S)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((3'-(cyclopropyloxy)-2-((1R)-2,2-dimethylcyclopentyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.48). A pre-mixed solution of 2M NaOH (0.3 mL), THF (0.5 mL), and MeOH (0.5 mL) was added to a vial containing 66.48H (0.0218 g, 0.0405 mmol). The mixture was stirred at room temperature and monitored with TLC and LC-MS. After 24 hours, the mixture was diluted with water and acidified with 1M aqueous HCl. The mixture was then extracted five times with EtOAc. The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel flash chromatography (0-40% EtOAc/hexane) to afford 66.48 as a colorless oil (13.9 mg, 65% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.42 (1 H, d, J=1.6 Hz), 7.34 (5 H, m), 7.03 (2 H, m), 6.93 (4 H, m), 5.09 (2 H, s), 3.79 (1 H, m),

3.15 (1 H, dd, J=10.4, 8.4 Hz), 2.86 (2 H, m), 2.43 (1 H, m), 2.12 (2 H, m), 1.86 (1 H, m), 1.72 (1 H, m), 1.51 (1 H, ddd, J=12.7, 8.0, 5.1 Hz), 1.40 (1 H, m), 1.10 (1 H, m), 0.84 (4 H, m), 0.74 (3 H, m), 0.64 (4 H, m), 0.49 (1 H, m), 0.36 (1 H, m), 0.22 (1 H, m). MS ESI (neg.) m/e: 523.0 (M-H)⁺.

[0789] **Example 66.49**

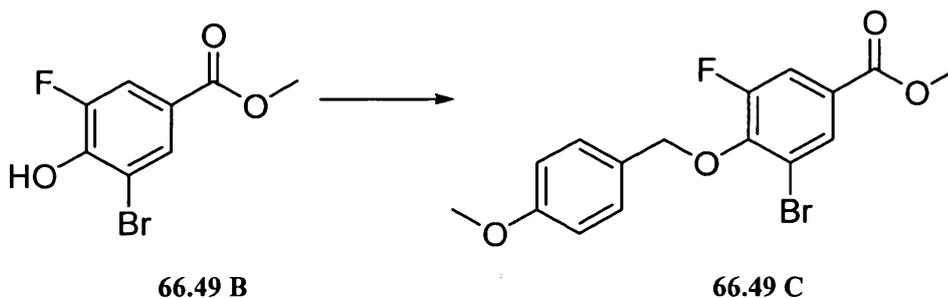


[0790] **Methyl 3-fluoro-4-hydroxybenzoate (66.49A)**. To a round bottom flask containing 3-fluoro-4-hydroxybenzoic acid (5.03 g, 32.22 mmol)(commercially available from Aldrich) was added a cold solution of MeOH (50.0 mL) and sulfuric acid (2.0 mL). The mixture was heated to 80°C and monitored with TLC. After 20.5 hours, the solvent was removed and the mixture was diluted with diethyl ether. The organic phase was washed carefully twice with saturated aqueous NaHCO₃ and once with brine. The organic phase was then dried over anhydrous sodium sulfate. After filtration, the organic solvent was removed in vacuo to afford **66.49A** as a white solid (4.79 g, 87% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.81 (2 H, m), 7.06 (1 H, t, J=8.4 Hz), 5.62 (1 H, d, J=4.3 Hz), 3.91 (3 H, s).

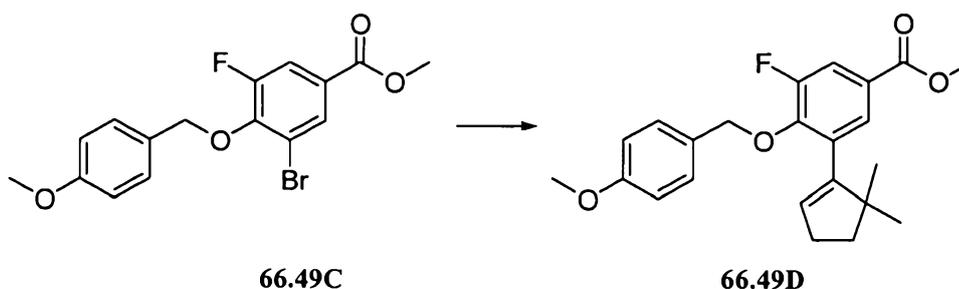


[0791] **Methyl 3-bromo-5-fluoro-4-hydroxybenzoate (66.49B)**. Bromine (1.60 mL, 31.1 mmol) was added dropwise with stirring over 30 minutes to an ice-cooled solution of **66.49A** (4.79 g, 28.1 mmol) in a 1:1 mixture of DCM (20 mL) and acetic acid (20 mL). Upon complete addition, the reaction mixture was allowed to warm to room temperature and monitored with TLC and LC-MS. After stirring at room temperature for

40 hours, the mixture was diluted with EtOAc, and then the resulting solution was washed twice with aqueous saturated Na_2SO_3 , once with water, and once with brine. After drying over anhydrous magnesium sulfate, filtration, and concentration, the white solid **66.49B** was obtained 6.69 g, 95% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 8.05 (1 H, m), 7.75 (1 H, dd, $J=10.6, 2.0$ Hz), 6.12 (1 H, s), 3.94 (3 H, s).

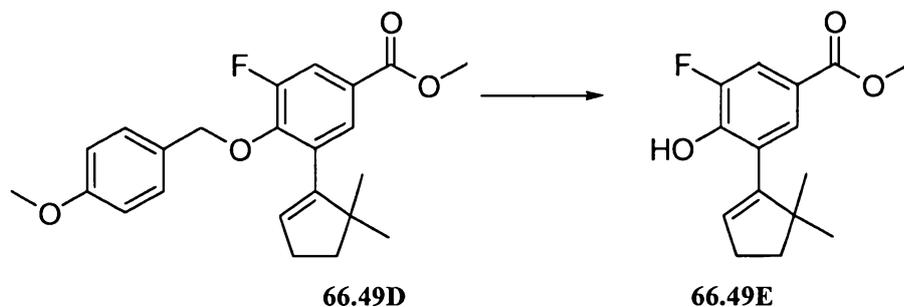


[0792] **Methyl 3-bromo-5-fluoro-4-((4-(methoxy)phenyl)methyl)oxybenzoate (66.49C)**. To a vial containing **66.49B** (0.64 g, 2.58 mmol) in 5.0 mL dry DMF was added cesium carbonate (1.10 g, 3.36 mmol). The mixture was stirred at room temperature for 10 minutes and then 4-methoxybenzyl bromide (0.45 mL, 3.1 mmol) was added. After 4 hours, the reaction was diluted with water and then extracted five times with EtOAc. The combined organic layers were then washed one time with brine and dried over anhydrous magnesium sulfate. The solid was filtered off, and the solvent was concentrated. The residue was purified by silica gel flash chromatography (0-40% EtOAc/hexane) to afford **66.49 C** as a white solid (679.1 mg, 71% yield). ^1H NMR (400 MHz, CDCl_3) δ ppm 8.02 (1 H, t, $J=2.0$ Hz), 7.72 (1 H, dd, $J=11.5, 2.2$ Hz), 7.42 (2 H, m, $J=8.6$ Hz), 6.90 (2 H, m), 5.20 (2 H, s), 3.91 (3 H, s), 3.82 (3 H, s).

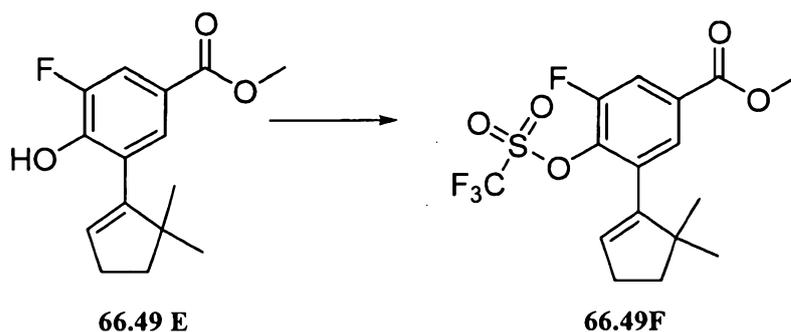


[0793] **Methyl 3-(5,5-dimethyl-1-cyclopenten-1-yl)-5-fluoro-4-((4-(methoxy)phenyl)methyl)oxybenzoate (66.49D)**. A stirred mixture of **66.49C** (1.63

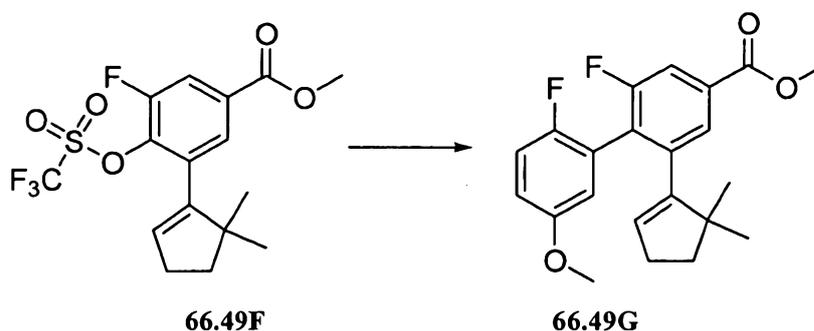
g, 4.420 mmol), ground S-Phos (0.36 g, 0.88 mmol), palladium acetate (0.10 g, 0.45 mmol), and potassium phosphate tribasic (2.35 g, 11.06 mmol) in DMF (13 mL) and water (0.4 mL) was purged with argon and placed under vacuum and the process repeated three times. Before heating, 2-(5,5-dimethylcyclopent-1-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**66.6C**) (1.47 g, 6.63 mmol) was added via syringe and then the mixture was heated to 75°C. After 18 hours, the reaction was cooled to room temperature, diluted with water, and extracted three times with EtOAc. The organic layers were combined and washed twice with brine. After drying over anhydrous sodium sulfate and filtration, the organic solvent was removed under reduced pressure. The residue was purified on a 40 g column of silica gel (0-10% EtOAc in hexanes) to afford **66.49D** as a white solid (1.12 g, 66% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.69 (1 H, dd, J=11.7, 2.3 Hz), 7.57 (1 H, dd, J=2.0, 1.2 Hz), 7.31 (2 H, m), 6.88 (2 H, m), 5.56 (1 H, t, J=2.5 Hz), 5.01 (2 H, s), 3.91 (3 H, s), 3.82 (3 H, s), 2.42 (2 H, td, J=7.0, 2.7 Hz), 1.86 (2 H, t, J=7.2 Hz), 1.06 (6 H, s).



[0794] **Methyl 3-(5,5-dimethyl-1-cyclopenten-1-yl)-5-fluoro-4-hydroxybenzoate (66.49E)**. To a flask containing **66.49D** (1.12 g, 2.93 mmol) was added a premixed solution of DCM (14 mL) and TFA (1 mL). The mixture was stirred at room temperature and monitored with TLC and LC-MS. After 1 hour, the reaction was diluted with DCM and then washed once with saturated aqueous sodium bicarbonate solution and brine. After washing, the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (SiO₂ gel 60, eluted with 0%-50% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide a colorless oil that solidified as **66.49E** and which was used without further purification (732.6 mg, 95 % yield).

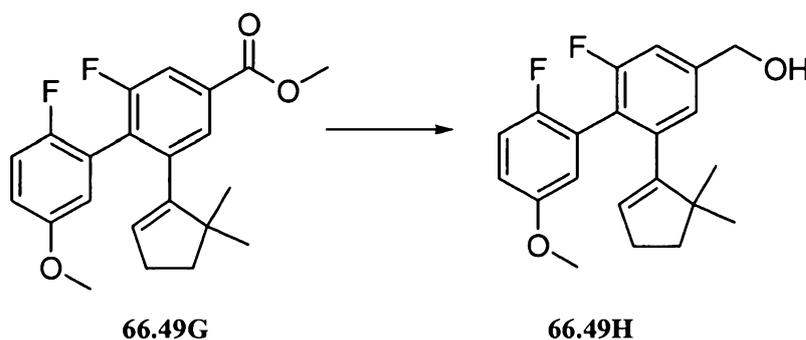


[0795] Methyl 3-(5,5-dimethyl-1-cyclopenten-1-yl)-5-fluoro-4-((trifluoromethyl)sulfonyloxy)benzoate (66.49F). To a stirred solution of **66.49E** (0.7326 g, 2.77 mmol) in dry DCM (15 mL) was added TEA (0.78 mL, 5.60 mmol) and 4-(dimethylamino)pyridine (0.0354 g, 0.29 mmol). After about 20 minutes, N-phenyl-bis(trifluoromethanesulfonimide) (1.20 g, 3.36 mmol) was added in portions. Upon complete addition, the solution was stirred at room temperature and monitored with TLC and LC-MS. After 19 hours, the organic solvent was removed under reduced pressure and the product thus obtained was then purified with silica gel chromatography using 0-10% EtOAc in hexanes to afford **66.49 F** as a colorless oil (946.4 mg, 86 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.82 (1 H, dd, J=9.9, 2.1 Hz), 7.75 (1 H, m), 5.87 (1 H, t, J=2.4 Hz), 3.95 (3 H, s), 2.49 (2 H, td, J=7.1, 2.4 Hz), 1.92 (2 H, t, J=7.0 Hz), 1.11 (6 H, s).

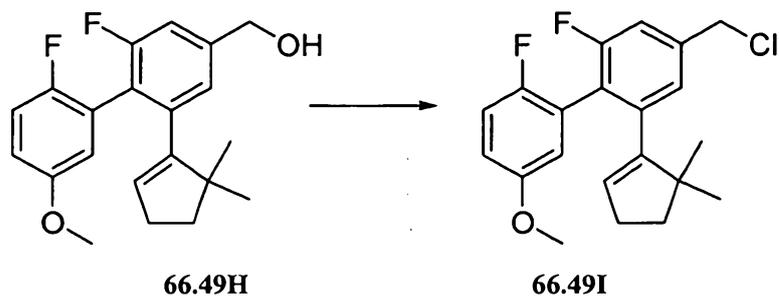


[0796] Methyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.49 G). A stirred mixture of **66.49 F** (0.9464 g, 2.39 mmol), ground S-Phos (0.1977 g, 0.482 mmol), palladium acetate (0.0555 g, 0.247 mmol), 2-fluoro-5-methoxyphenylboronic acid (0.8114 g, 4.77 mmol) (commercially available from Aldrich), and potassium phosphate tribasic (1.2888 g, 6.072 mmol) in dry DMF (7.000 mL) was purged with argon and placed under vacuum

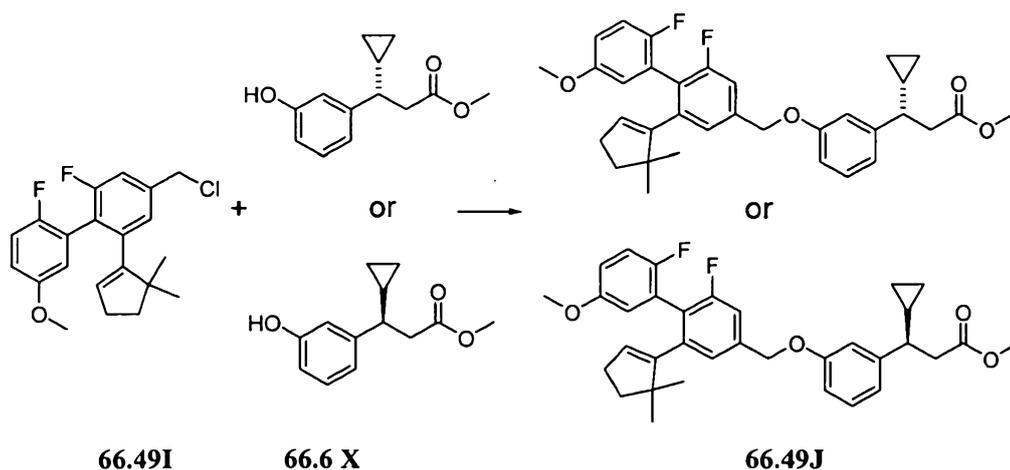
and the process repeated three times. The mixture was then heated to 75°C and the reaction was stirred for 21 hours. The reaction was then cooled to room temperature, diluted with water and extracted three times with EtOAc. The organic layers were combined and washed twice with brine. After drying over anhydrous sodium sulfate and filtration, the organic solvent was removed under reduced pressure. The residue was purified on an 80 g column of silica gel (0-20% EtOAc in hexanes) to afford **66.49G** as a colorless oil that was used without further purification (850.5 mg, 95% yield). MS ESI (pos.) m/e: 373.0 (M+H)⁺.



[0797] **(2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (66.49H)**. To a cooled solution of **66.49 G** (0.1435 g, 0.385 mmol) in dry THF (9 mL) at 0 °C was added LAH (1.0 M in THF)(0.8 mL, 0.80 mmol) dropwise. Upon complete addition, the reaction was maintained at 0°C and was monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction (gas evolution occurred), and the resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified by flash chromatography (SiO₂ gel 60, eluted with 0%-50% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **66.49H** as a colorless oil (114.9 mg, 87% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.12 (1 H, dd, J=9.8, 1.6 Hz), 7.04 (2 H, m), 6.84 (1 H, dt, J=9.0, 3.5 Hz), 6.74 (1 H, dd, J=5.5, 3.1 Hz), 5.50 (1 H, t, J=2.3 Hz), 4.74 (2 H, s), 3.76 (3 H, s), 2.24 (2 H, td, J=7.0, 2.3 Hz), 1.75 (5 H, m), 0.97 (3 H, s), 0.78 (3 H, s).

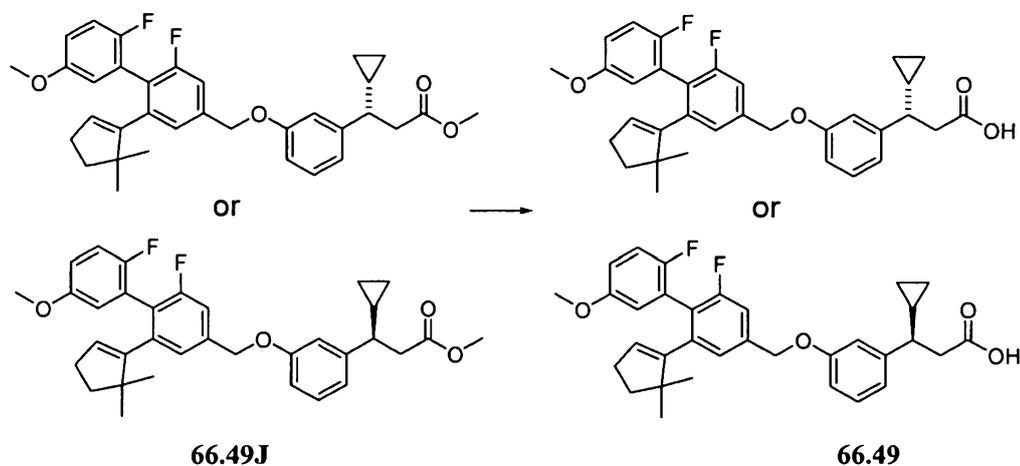


[0798] **4-(Chloromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl (66.49I)**. To a solution of **66.49H** (0.1149 g, 0.334 mmol) in dry DCM (4 mL) and dry DMF (0.03 mL) was added thionyl chloride (0.05 mL, 0.685 mmol) at 0 °C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **66.49I** as a colorless oil (35.6 mg, 29% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.14 (1 H, dd, J=9.4, 1.6 Hz), 7.06 (1 H, s), 7.00 (1 H, t, J=9.0 Hz), 6.85 (1 H, dt, J=9.0, 3.7 Hz), 6.74 (1 H, dd, J=5.5, 3.1 Hz), 5.53 (1 H, t, J=2.3 Hz), 4.61 (2 H, s), 3.76 (3 H, s), 2.25 (2 H, td, J=7.1, 2.5 Hz), 1.73 (2 H, m), 0.97 (3 H, s), 0.78 (3 H, s).



[0799] **Methyl (3S)-3-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.49 J)**. To a vial containing **66.6X** (0.0191 g, 0.0867 mmol) in 1.00 mL dry DMF was added cesium carbonate (0.0363 g, 0.111 mmol). The mixture was stirred at room temperature for 10

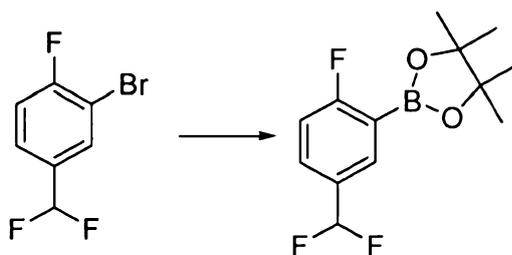
minutes and then **66.49I** (0.0356 g, 0.0981 mmol) was added. After 22 hours, the reaction was diluted with water and then extracted five times with EtOAc. The organic layers were combined and then washed one time with brine and dried over anhydrous magnesium sulfate. The solid was filtered off, and the mixture was concentrated. The residue was purified by silica gel flash chromatography (0-50% EtOAc/hexane) to afford **66.49J** as a colorless oil (43.2 mg, 91% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.29 (2 H, m), 7.10 (1 H, s), 6.99 (1 H, t, J=8.8 Hz), 6.92 (4 H, m), 6.75 (1 H, dd, J=5.5, 3.1 Hz), 5.52 (1 H, t, J=2.3 Hz), 5.09 (2 H, s), 3.76 (3 H, s), 3.62 (3 H, s), 2.83 (2 H, m), 2.43 (1 H, m), 2.25 (2 H, td, J=7.0, 2.3 Hz), 1.74 (2 H, m), 1.09 (4 H, m), 0.78 (3 H, s), 0.64 (1 H, m), 0.49 (1 H, m), 0.28 (1 H, dq, J=9.7, 4.8 Hz), 0.20 (1 H, m).



[0800] **(3S)-3-Cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.49)**. A pre-mixed solution of 2M NaOH (0.5 mL, 1.00 mmol), MeOH (1.5 mL), and THF (1.5 mL) was added to a vial containing **66.49J** (0.0432 g, 0.0790 mmol). The resulting solution was stirred at room temperature and monitored with TLC and LC-MS. After 24 hours, the mixture was diluted with water and acidified with 1M aqueous HCl solution and then extracted five times with EtOAc. The organic phase was dried over anhydrous magnesium sulfate and then was filtered and concentrated. The residue was purified by silica gel flash chromatography (0-40% EtOAc/hexane) to afford **66.49** as a colorless oil (36.1 mg, 86% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.29 (3 H, m), 7.09 (1 H, d,

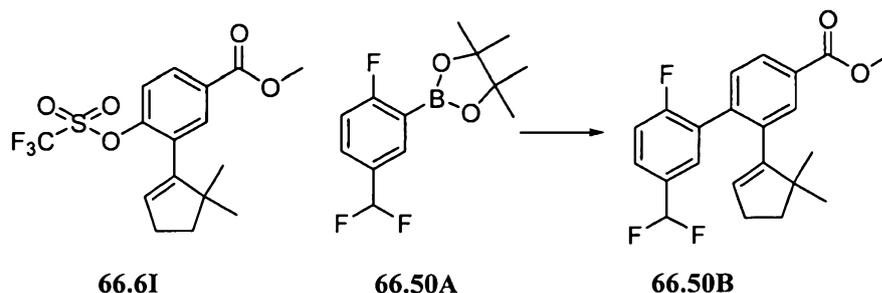
J=1.2 Hz), 6.99 (1 H, t, J=8.8 Hz), 6.91 (4 H, m), 6.75 (1 H, dd, J=5.9, 3.1 Hz), 5.52 (1 H, t, J=2.2 Hz), 5.09 (2 H, s), 2.86 (2 H, m), 2.42 (1 H, m), 2.24 (2 H, td, J=7.0, 2.3 Hz), 1.74 (2 H, m), 1.08 (4 H, m), 0.77 (3 H, s), 0.66 (1 H, m), 0.44 (1 H, tt, J=8.9, 4.6 Hz), 0.30 (1 H, dq, J=9.6, 4.8 Hz), 0.22 (1 H, m). MS ESI (neg.) m/e: 531.0 (M-H)⁺.

[0801] **Example 66.50**

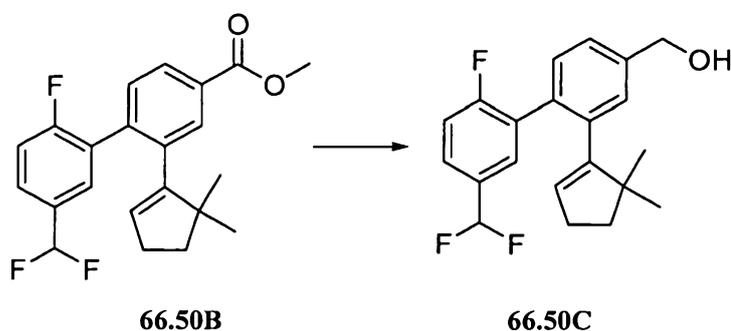


66.50A

[0802] **2-(5-(Difluoromethyl)-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (66.50A).** A stirred mixture of 1-bromo-5-difluoromethyl-2-fluorobenzene (commercially available from Oakwood Products, Inc.) (2.0231 g, 8.991 mmol), bis(pinacolato)diboron (2.5123 g, 9.893 mmol), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) DCM adduct (0.3688 g, 0.4516 mmol), and potassium acetate (2.6504 g, 27.01 mmol) in dry 1,4-dioxane (35 mL) was purged with argon and placed under vacuum and the purging vacuum process repeated three times. The mixture was heated to 90°C and monitored with LC-MS and TLC. After 18 hours, the reaction was cooled to room temperature and then filtered through Celite. The organic solvent was removed under reduced pressure, and the residue was purified on a 40 g column of silica gel (0-10% EtOAc in hexanes) to afford **66.50A** as a colorless oil that was used without further purification (1.6019 g, 65% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.89 (1 H, td, J=2.7, 1.2 Hz), 7.63 (1 H, m), 7.09 (1 H, t, J=8.6 Hz), 6.62 (1H, t), 1.35 (12 H, s).

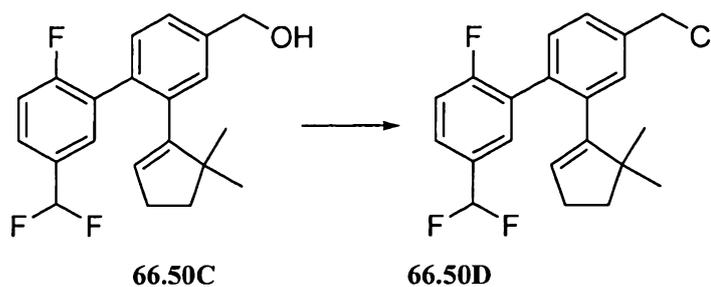


[0803] Methyl 5'-(difluoromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-carboxylate (66.50B). To a stirred solution of **66.6I** (1.1209 g, 2.962 mmol) in dry DMF (10 mL) at 23°C was added potassium carbonate (1.2262 g, 8.872 mmol) and then tetrakis(triphenylphosphine)palladium (0.3408 g, 0.2949 mmol). The mixture was purged with argon and placed under vacuum and the purging and vacuum process repeated three times. Before heating, **66.50A** (1.6019 g, 5.888 mmol) was added via syringe and then the mixture was heated to 90 °C. After 19 hours, LC-MS showed that the reaction was complete. The mixture was cooled to room temperature and then diluted with water. After extracting three times with EtOAc, the mixture was concentrated in vacuo and then purified on silica gel (0%-10% EtOAc/hexane) to afford **66.50B** as a clear oil (994.4 mg, 90% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.00 (1 H, dd, J=8.0, 1.8 Hz), 7.94 (1 H, d, J=1.6 Hz), 7.50 (3 H, m), 7.16 (1 H, t, J=9.0 Hz), 6.63 (1H, t), 5.53 (1 H, s), 3.96 (3 H, s), 2.25 (2 H, td, J=7.0, 2.3 Hz), 1.65 (2 H, t, J=7.0 Hz), 0.85 (6 H, s).

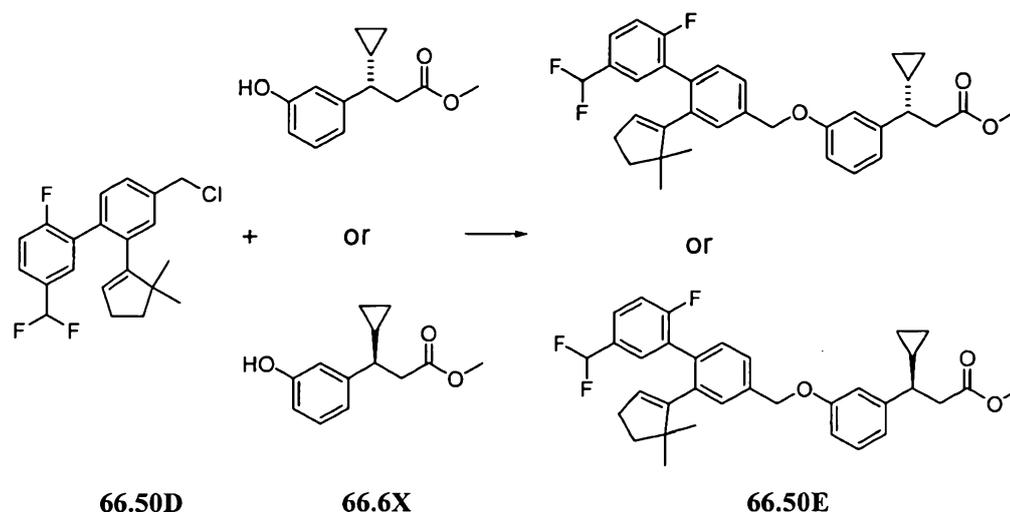


[0804] (5-(Difluoromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-yl)methanol (66.50C). To a cooled solution of **66.50B** (0.2349 g, 0.6274 mmol) in dry THF (5 mL) at 0 °C was added LAH (1.0 M in THF)(1.3 mL, 1.3 mmol) dropwise. Upon complete addition, the reaction was maintained at 0°C and was monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the

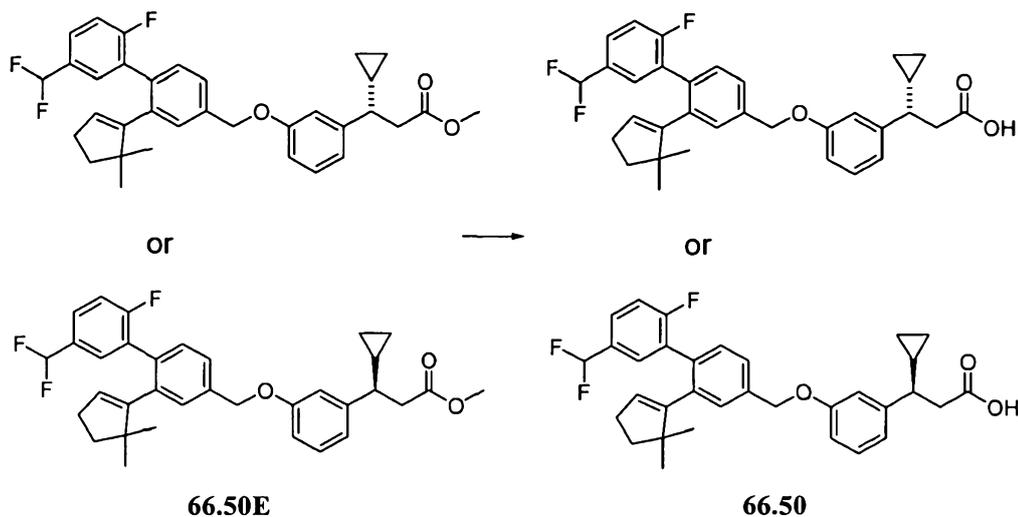
reaction (gas evolution occurred). The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-50% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to a colorless oil as **66.50C** (166.6 mg, 77% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.47 (2 H, m), 7.38 (2 H, m), 7.14 (1 H, t, J=9.0 Hz), 6.62 (1H, t), 5.50 (1 H, td, J=2.4, 1.0 Hz), 4.76 (2 H, s), 2.23 (2 H, td, J=7.0, 2.3 Hz), 1.74 (3 H, m), 0.85 (6 H, s).



[0805] **4-(Chloromethyl)-5'-(difluoromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl (66.50D)**. To a solution of **66.50C** (0.1666 g, 0.481 mmol) in dry DCM (3 mL) and dry DMF (0.06 mL) was added thionyl chloride (0.07 mL, 0.96 mmol) at 0°C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **66.50D** (172.1 mg, 98% yield). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.46 (2 H, m), 7.39 (1 H, m), 7.33 (1 H, m), 7.28 (1 H, d, J=1.7 Hz), 7.17 (1 H, m), 6.62 (1H, t), 5.51 (1 H, td, J=2.3, 1.0 Hz), 4.64 (2 H, s), 2.24 (2 H, td, J=7.1, 2.4 Hz), 1.68 (2 H, m), 0.85 (6 H, s).

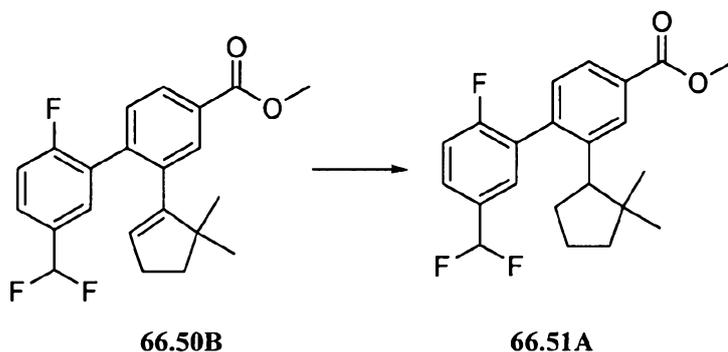


[0806] **Methyl (3S)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.50E).** To a vial containing **66.6X** (0.0321 g, 0.146 mmol) in 1.00 mL dry DMF was added cesium carbonate (0.0577 g, 0.177 mmol). The mixture was stirred at room temperature for 10 minutes and then **66.50D** (0.0604 g, 0.166 mmol) was added. After 22 hours, the reaction was diluted with water and then extracted five times with EtOAc. The combined organic layers were then washed one time with brine and dried over anhydrous magnesium sulfate. The solid was filtered off, and the solvent was concentrated. The residue was purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **66.50E** (60.8 mg, 76% yield). MS ESI (pos.) m/e: 566.0 (M+H₂O)⁺.

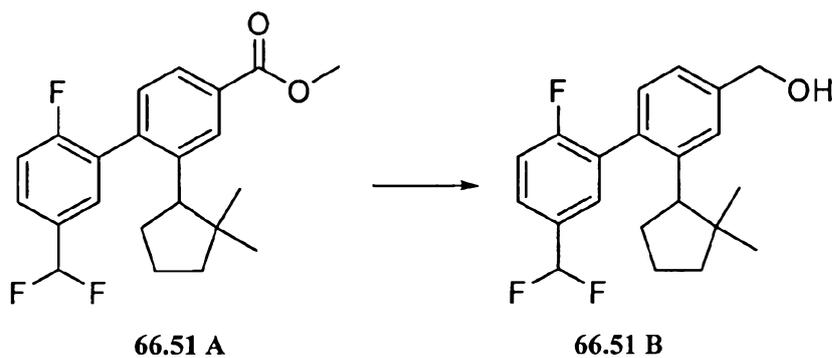


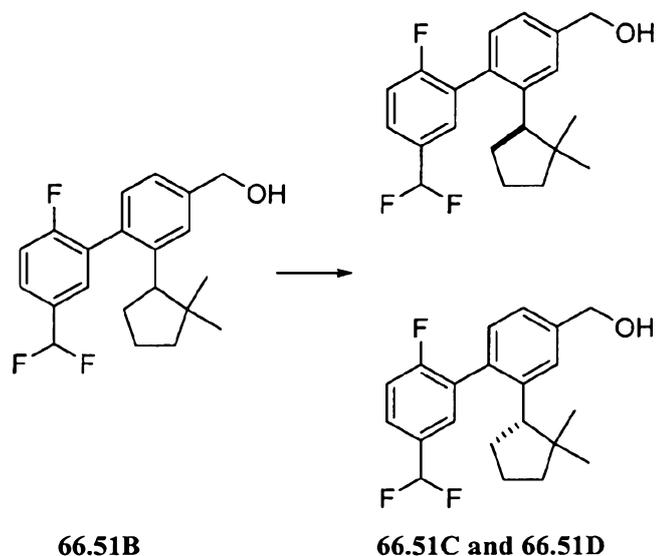
[0807] **(3S)-3-Cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.50).** A pre-mixed solution of 2M NaOH (0.5 mL, 1.00 mmol), MeOH (1 mL), and THF (1 mL) was added to a vial containing **66.50E** (0.0608 g, 0.111 mmol). The resulting solution was stirred at room temperature and monitored with TLC and LC-MS. After 24 hours, the mixture was diluted with water, acidified with 1M aqueous HCl, and then extracted five times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate and then filtered and concentrated. The residue was purified by silica gel flash chromatography (0-40% EtOAc/hexane) to afford **66.50** as a colorless oil (47.8 mg, 81% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.49 (3 H, m), 7.37 (2 H, m), 7.25 (1 H, t, J=7.8 Hz), 7.15 (1 H, t, J=8.8 Hz), 6.94 (3 H, m), 6.77 (1H, t), 5.51 (1 H, m), 5.12 (2 H, s), 2.87 (2 H, m), 2.44 (1 H, m), 2.24 (2 H, td, J=7.0, 2.3 Hz), 1.64 (2 H, t, J=7.0 Hz), 1.10 (1 H, m), 0.84 (6 H, s), 0.65 (1 H, m), 0.49 (1 H, m), 0.31 (1 H, dq, J=9.6, 4.8 Hz), 0.17 (1 H, dq, J=9.7, 5.0 Hz). MS ESI (neg.) m/e: 532.9 (M-H)⁺.

[0808] **Example 66.51**

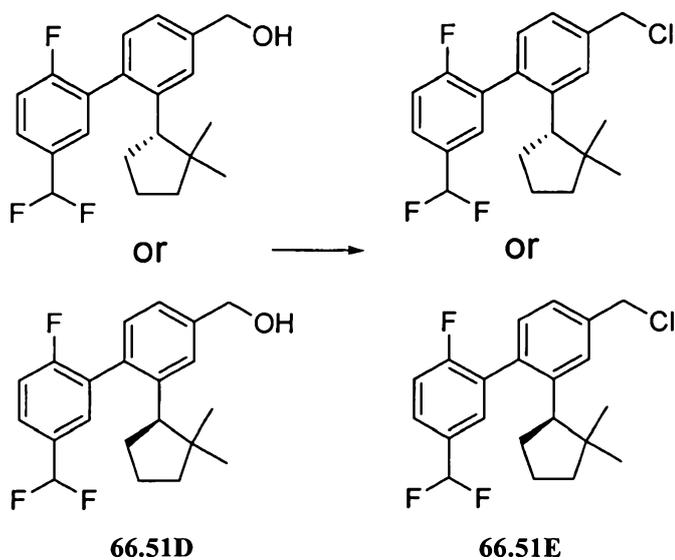


[0809] Methyl 5'-(difluoromethyl)-2-(2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-carboxylate (66.51A). To a dry flask containing **66.50B** (0.8621 g, 2.303 mmol) in dry MeOH (10 mL) and EtOAc (2 mL) was added palladium (10% wt. on activated carbon)(0.2455 g, 0.2307 mmol). After purging, the mixture was stirred under an atmosphere of hydrogen at room temperature. The reaction was monitored with TLC and LC-MS. After 22.5 hours, the reaction was filtered through Celite. After concentration, the residue was identified as **66.51A** and was used without purification (863 mg, 99% yield). MS ESI (pos.) m/e: 376.9 (M+H)⁺.



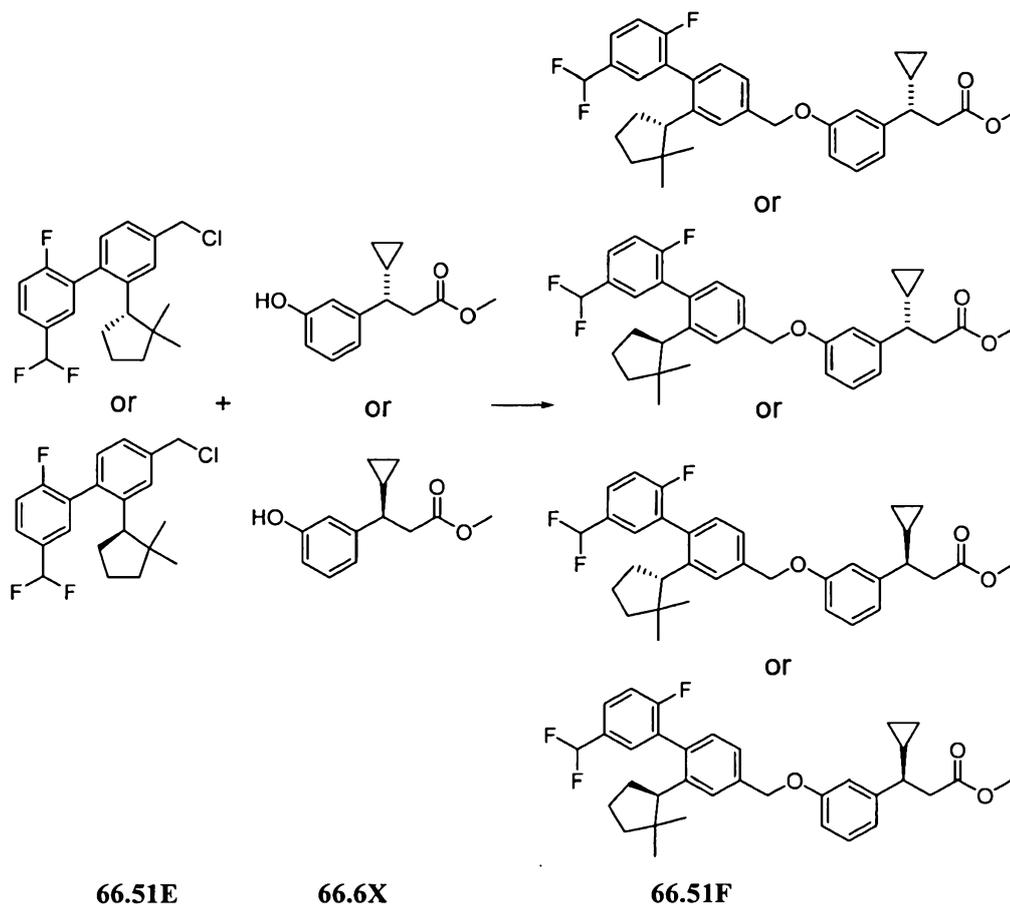


[0810] (5'-(Difluoromethyl)-2-(2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methanol (**66.51B**). To a cooled solution of **66.51A** (0.8631 g, 2.293 mmol) in dry THF (15.4 mL) at 0 °C was added LAH (1.0 M in THF)(4.6 mL, 4.6 mmol) dropwise. Upon complete addition, the reaction was maintained at 0°C and was monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction (gas evolution occurred). The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-100% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to a colorless oil as **66.51B** (617.1 mg, 77% yield). MS ESI (pos.) m/e: 331.0 (M-H₂O)⁺. Chiral separation of **66.51B** was accomplished on a Chiracel-OD column (4% IPA in hexane) to provide **66.51C** (peak 1) and **66.51D** (peak 2). Both enantiomers were used to synthesize example compounds, and both enantiomers gave active compounds.



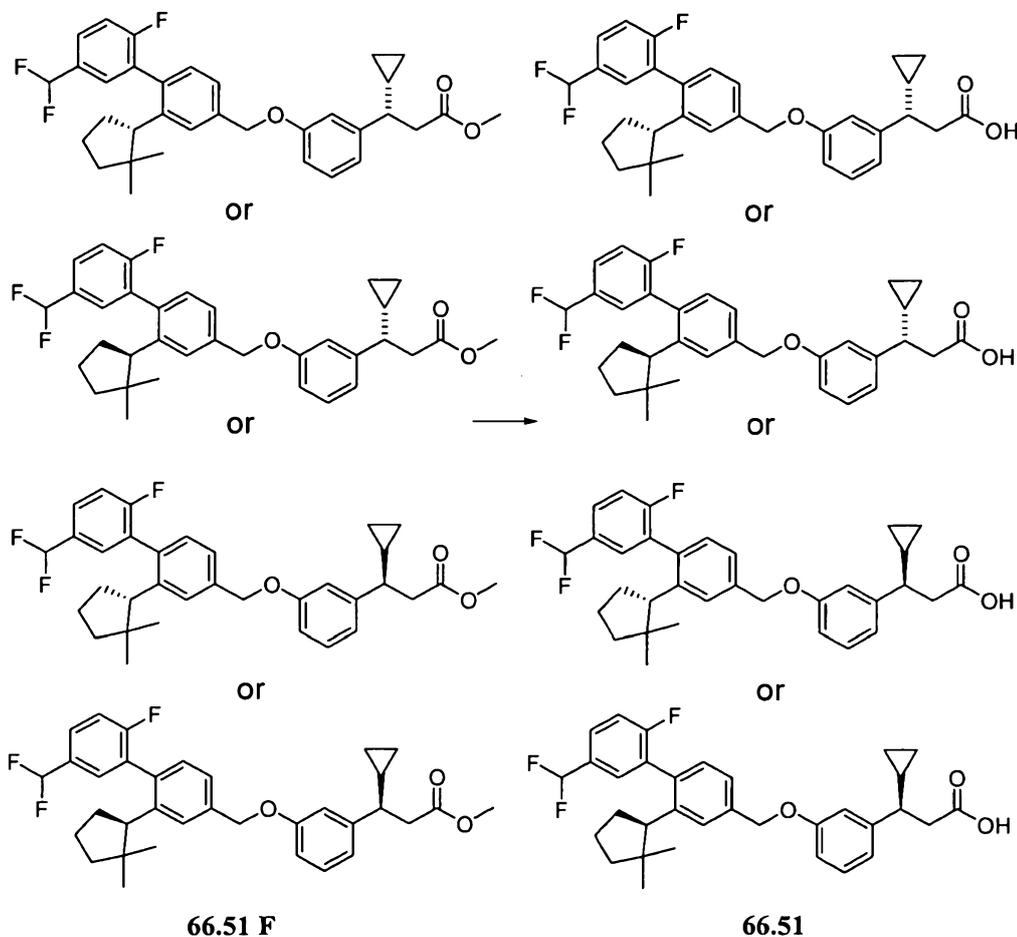
[0811] 4-(Chloromethyl)-5'-(difluoromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl or 4-(chloromethyl)-5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl (**66.51E**).

To a solution of **66.51D** (0.2882 g, 0.827 mmol) in dry DCM (10.5 mL) and dry DMF (0.08 mL) was added thionyl chloride (0.12 mL, 1.65 mmol) at 0 °C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **66.51E** (272.1 mg, 90% yield).



[0812] **Methyl (3S)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3S)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.51F).** To a vial containing **66.6X** (0.0338 g, 0.153 mmol) in 1.00 mL dry DMF was added cesium carbonate (0.0689 g, 0.211 mmol). The mixture was stirred at room temperature for 10 minutes and then **66.51E** (0.0622 g, 0.170 mmol) was added. After 22 hours, the reaction was diluted with water and then extracted five times with EtOAc. The combined organic layers were then washed one time with brine and dried over anhydrous magnesium sulfate. The solid was filtered off, and the solvent was concentrated. The

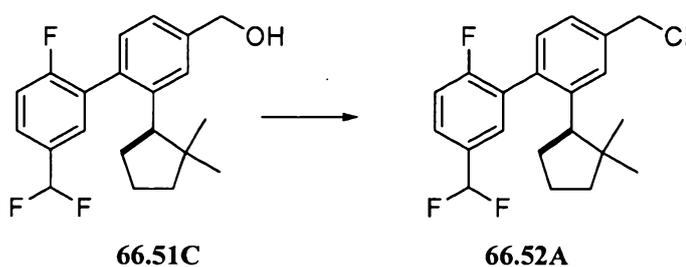
residue was purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **66.51F** (64.9 mg, 77% yield). MS ESI (pos.) m/e: 568.0 (M+H₂O)⁺.



[0813] (3S)-3-Cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (**66.51**). A pre-mixed solution of 2M NaOH (0.5 mL, 1.00 mmol), THF (1 mL), and MeOH (1 mL) was added to a vial containing **66.51F** (0.0649 g, 0.118 mmol). The resulting solution was stirred at room temperature and monitored with TLC and LC-MS. After 24 hours, the mixture was diluted with water,

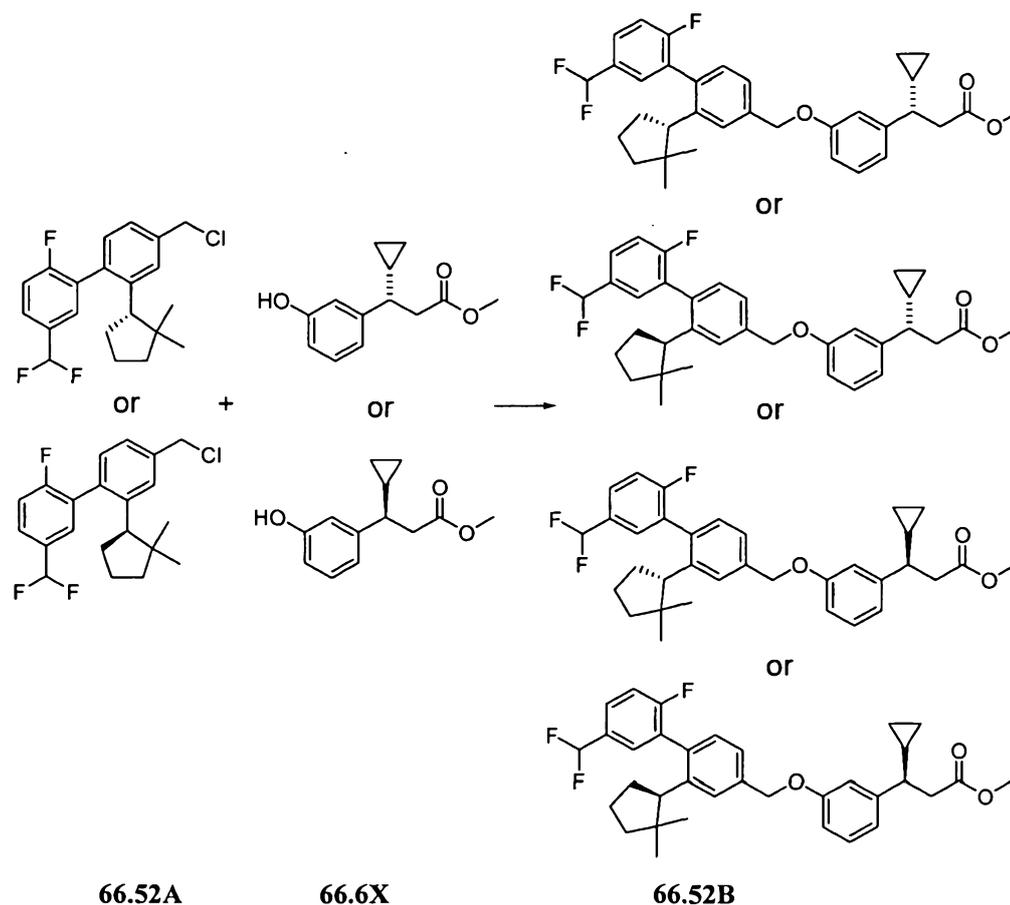
acidified with 1M aqueous HCl, and then extracted five times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate and then filtered and concentrated. The residue was purified with reverse phase HPLC using 30-90% Solvent B(0.1% TFA in acetonitrile) to afford **66.51** (36.9 mg, 58% yield). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 7.55 (4 H, m), 7.29 (3 H, m), 6.91 (3 H, m), 6.53 (1H, t), 5.12 (2 H, m), 2.90 (3 H, m), 2.37 (1 H, dt, $J=9.5, 7.6$ Hz), 2.22 (2 H, m), 1.85 (1 H, m), 1.72 (1 H, m), 1.58 (1 H, m), 1.42 (1 H, m), 1.13 (1 H, m), 0.76 (3 H, m), 0.65 (2 H, m), 0.51 (2 H, m), 0.49 (1 H, m), 0.37 (1 H, m), 0.22 (1 H, m). MS ESI (neg.) m/e : 535.0 (M-H) $^+$.

[0814]

Example 66.52

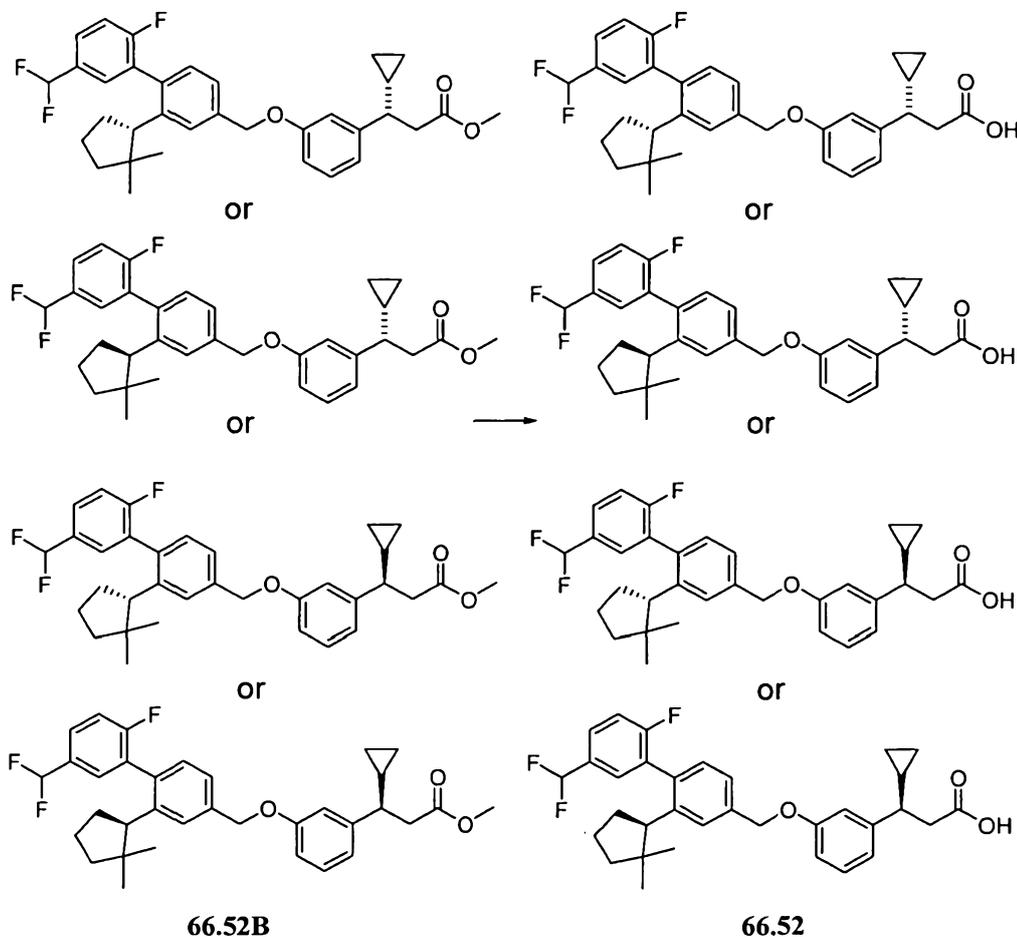
[0815]

4-(Chloromethyl)-5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl (66.52A). To a solution of **66.51C** (0.2798 g, 0.803 mmol) in dry DCM (10 mL) and dry DMF (0.076 mL) was added thionyl chloride (0.12 mL, 1.65 mmol) at 0°C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **66.52A** (282.5 mg, 96% yield).



[0816] **Methyl (3S)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3S)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.52B).** To a vial containing **66.6X** (0.0258 g, 0.117 mmol) in 1.00 mL dry DMF was added cesium carbonate (0.0466 g, 0.143 mmol). The mixture was stirred at room temperature for 10 minutes and then **66.52A** (0.0478 g, 0.130 mmol) was added. After 22 hours, the reaction was diluted with water and then extracted five times with EtOAc. The combined organic layers were then washed one time with brine and dried over anhydrous magnesium sulfate. The solid was filtered off, and the solvent was concentrated. The

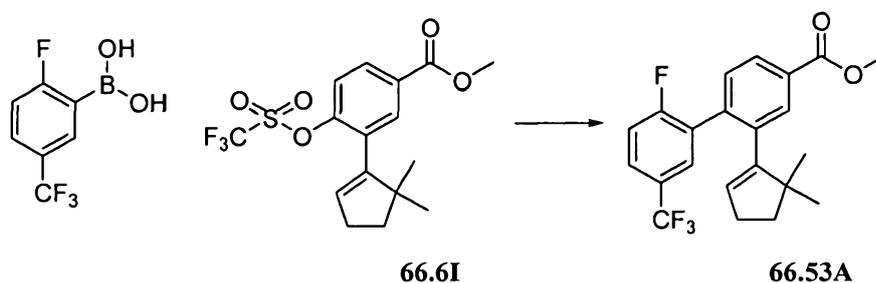
residue was purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **66.52B** (57.6 mg, 89% yield). MS ESI (pos.) m/e: 568.3 (M+H₂O)⁺.



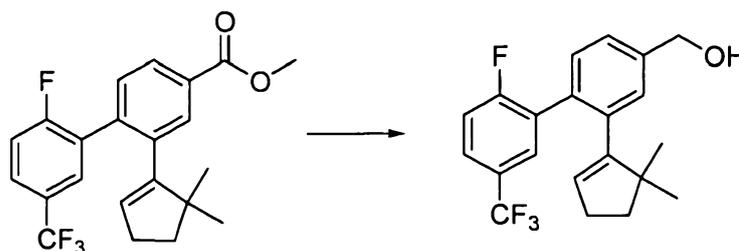
[0817] **(3S)-3-Cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid** or **(3S)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid** or **(3R)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid** or **(3R)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid** (**66.52**). A pre-mixed solution of 2M NaOH (0.5 mL, 1.00 mmol), THF (1 mL), and MeOH (1 mL) was added to a vial containing **66.52B** (0.0576 g, 0.105 mmol). The mixture was stirred at room temperature and monitored with TLC and LC-MS. After 24 hours, the mixture was diluted with water, acidified with

1M aqueous HCl, and then extracted five times with EtOAc. The combined organic layers were then dried over anhydrous magnesium sulfate and then filtered and concentrated. The residue was purified with reverse phase HPLC using 30-90% Solvent B(0.1% TFA in acetonitrile) to afford **66.52** (29.3 mg, 52% yield). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 7.39 (4 H, m), 7.13 (3 H, m), 6.74 (3 H, m), 6.64 (1H, t), 4.98 (2 H, m), 2.72 (3 H, m), 2.27 (1 H, m), 2.07 (2 H, m), 1.69 (1 H, m), 1.56 (1 H, m), 1.40 (1 H, m), 1.26 (1 H, m), 0.94 (1 H, m), 0.56 (3 H, m), 0.48 (2 H, m), 0.34 (2 H, m), 0.32 (1 H, m), 0.18 (1 H, m), -0.01 (1 H, dq, $J=9.7, 5.0$ Hz). MS ESI (neg.) m/e : 535.0 (M-H) $^+$.

[0818] **Example 66.53**



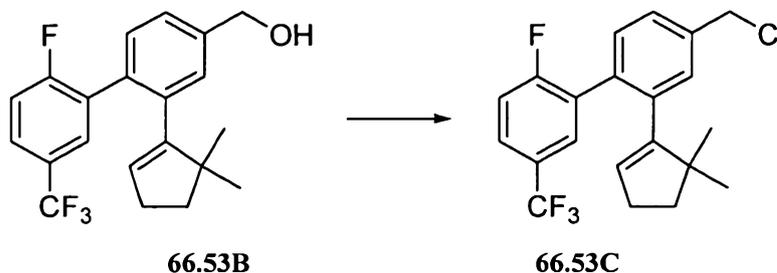
[0819] **Methyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(trifluoromethyl)-1,1'-biphenyl-4-carboxylate (66.53A)**. To a stirred solution of **66.6I** (0.7595 g, 2.007 mmol) in DMF (5 mL) at 23 °C was added 2-fluoro-5-(trifluoromethyl)phenylboronic acid (commercially available from Aldrich Chemical Company, Inc.) (0.8352 g, 4.017 mmol) and potassium carbonate (0.8357 g, 6.047 mmol) followed by tetrakis(triphenylphosphine)palladium (0.2364 g, 0.2046 mmol). The mixture was heated to 90°C. After 17 hours, LCMS-showed that the reaction was complete. The mixture was cooled to room temperature and then diluted with water. After extracting three times with EtOAc, the mixture was concentrated in vacuo and then purified on silica gel (0%-10% EtOAc/hexane) to afford **66.53A** as a clear oil that was used without further purification (414.2 mg, 53% yield).



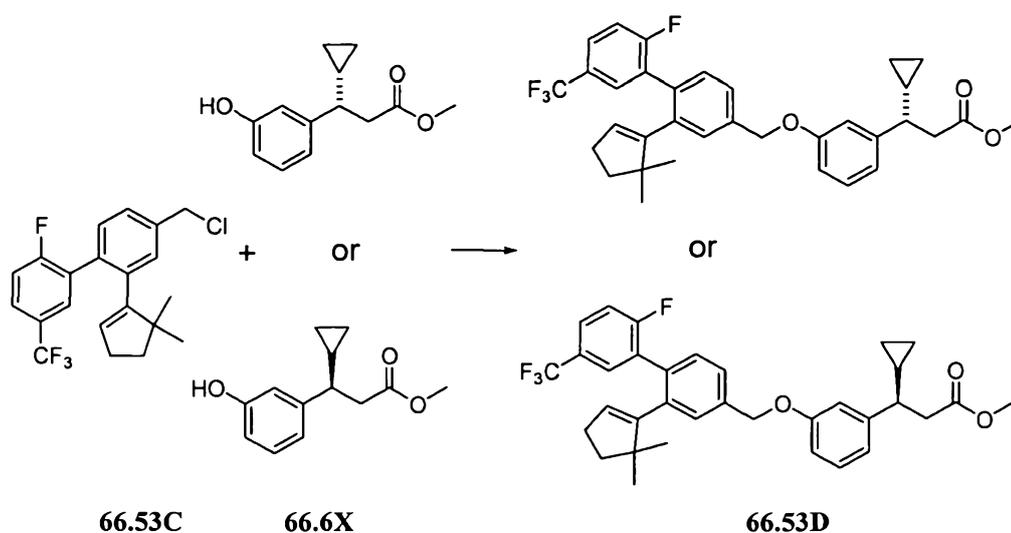
66.53A

66.53B

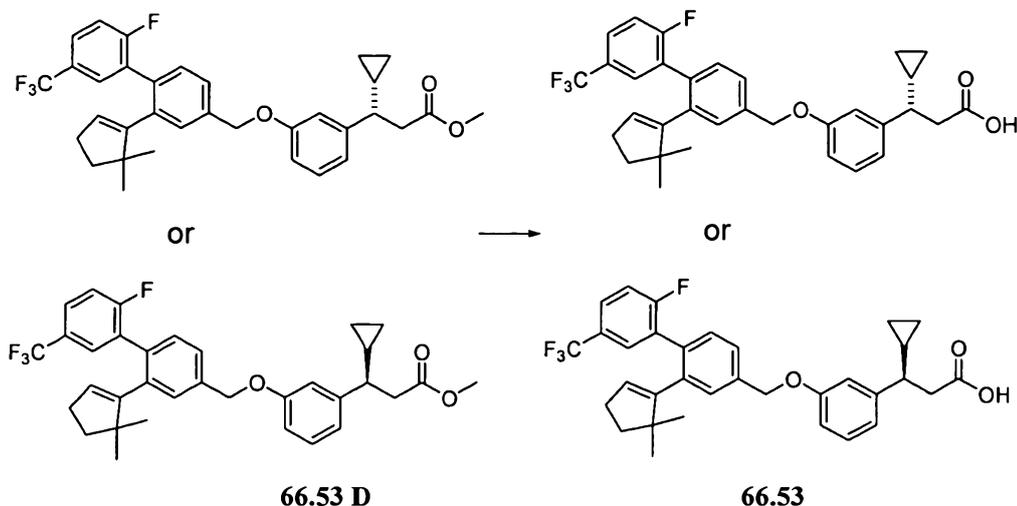
[0820] **(2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(trifluoromethyl)-1,1'-biphenyl-4-yl)methanol (66.53B)**. To a cooled solution of **66.53A**(0.4142 g, 1.056 mmol) in dry THF (7.8 mL) at 0 °C was added LAH (1.0 M in THF)(2.2 mL, 2.200 mmol) dropwise. Upon complete addition, the reaction was maintained at 0°C and was monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction (gas evolution occurred). The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified by flash chromatography (SiO₂ gel 60, eluted with 0%-100% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to afford **66.53B** as a colorless oil (257.4 mg, 67 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.61 (2 H, m), 7.40 (2 H, m), 7.17 (1 H, t, J=8.8 Hz), 5.52 (1 H, m), 4.77 (2 H, s), 2.24 (2 H, td, J=7.0, 2.3 Hz), 1.71 (3 H, m), 0.84 (6 H, s).



[0821] **4-(Chloromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(trifluoromethyl)-1,1'-biphenyl (66.53C)**. To a solution of **66.53B** (0.2574 g, 0.706 mmol) in dry DCM (10 mL) and dry DMF (0.07 mL) was added thionyl chloride (0.11 mL, 1.51 mmol) at 0 °C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **66.53C** (242.8 mg, 90 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.60 (2 H, m), 7.40 (1 H, m), 7.35 (2 H, m), 7.21 (1 H, m), 5.52 (1 H, td, J=2.4, 0.9 Hz), 4.66 (2 H, m), 2.24 (2 H, td, J=7.0, 2.3 Hz), 1.68 (2 H, m), 0.84 (6 H, s).

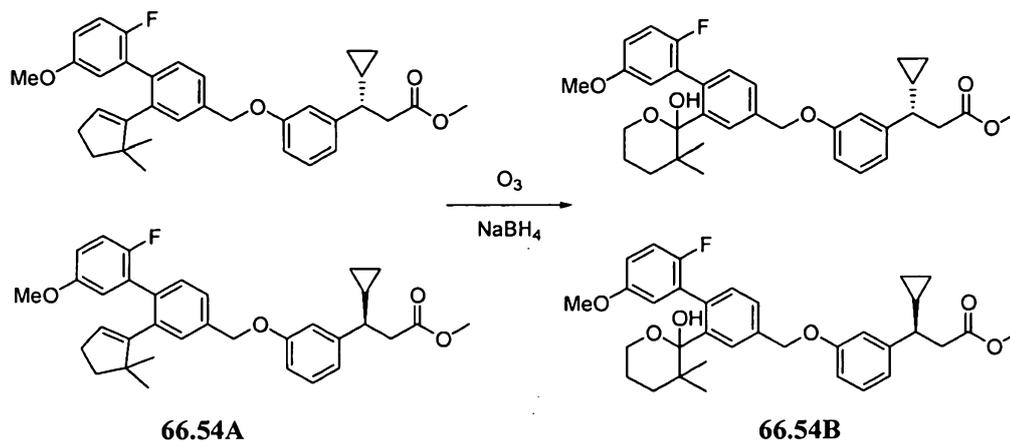


[0822] **Methyl (3S)-3-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(trifluoromethyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(trifluoromethyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.53D).** To a vial containing **66.6X** (0.0358 g, 0.163 mmol) in 1.00 mL dry DMF was added cesium carbonate (0.0674 g, 0.207 mmol). The mixture was stirred at room temperature for 10 minutes and then **66.53C** (0.0699 g, 0.183 mmol) was added. After 22 hours, the reaction was diluted with water and then extracted five times with EtOAc. The organic extraction was then washed one time with brine and dried over anhydrous magnesium sulfate. The solid was filtered off, and the solvent was concentrated. The residue was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to afford **66.53D** (64.2 mg, 70 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.62 (2 H, m), 7.46 (1 H, m), 7.35 (2 H, dd, J=10.8, 1.4 Hz), 7.29 (1 H, m), 7.17 (1 H, t, J=8.8 Hz), 6.93 (3 H, m), 5.51 (1 H, t, J=2.0 Hz), 5.11 (2 H, s), 3.62 (2 H, s), 2.82 (2 H, m), 2.44 (1 H, m), 2.24 (2 H, td, J=7.0, 2.7 Hz), 1.64 (2 H, t, J=7.0 Hz), 1.33 (4 H, m), 0.93 (6 H, m), 0.65 (1 H, m), 0.48 (1 H, m), 0.27 (1 H, dq, J=9.4, 4.8 Hz), 0.21 (1 H, m).

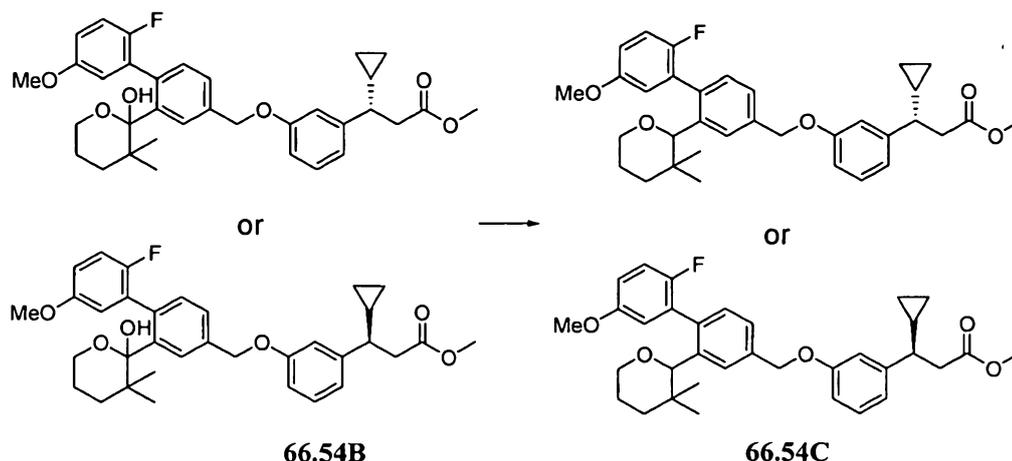


[0823] (3S)-3-Cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(trifluoromethyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(trifluoromethyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (**66.53**). A pre-mixed solution of 2M NaOH (0.5 mL, 1.00 mmol), MeOH (1 mL), and THF (1 mL) was added to a vial containing **66.53D** (0.0642 g, 0.113 mmol). This solution was stirred at room temperature and monitored with TLC and LC-MS. After 24 hours, the mixture was diluted with water, acidified with 1M aqueous HCl, and then extracted five times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate and then were filtered and concentrated. The residue was purified with reverse phase HPLC using 30-90% Solvent B (0.1% TFA in ACN) to afford **66.53** (46.3 mg, 74% yield). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.61 (2 H, m), 7.43 (1 H, dd, J=7.8, 1.7 Hz), 7.37 (2 H, m), 7.28 (3 H, m), 7.17 (1 H, t, J=8.8 Hz), 6.92 (3 H, m), 5.50 (1 H, m), 5.11 (2 H, s), 2.86 (2 H, m), 2.42 (1 H, m), 2.23 (2 H, td, J=7.0, 2.3 Hz), 1.63 (2 H, t, J=7.0 Hz), 1.08 (1 H, m), 0.82 (6 H, s), 0.65 (1 H, m), 0.48 (1 H, m), 0.30 (1 H, dq, J=9.6, 4.9 Hz), 0.17 (1 H, dddd, J=9.7, 5.1, 5.0, 4.9 Hz). MS ESI (neg.) m/e: 550.9 (M-H)⁻.

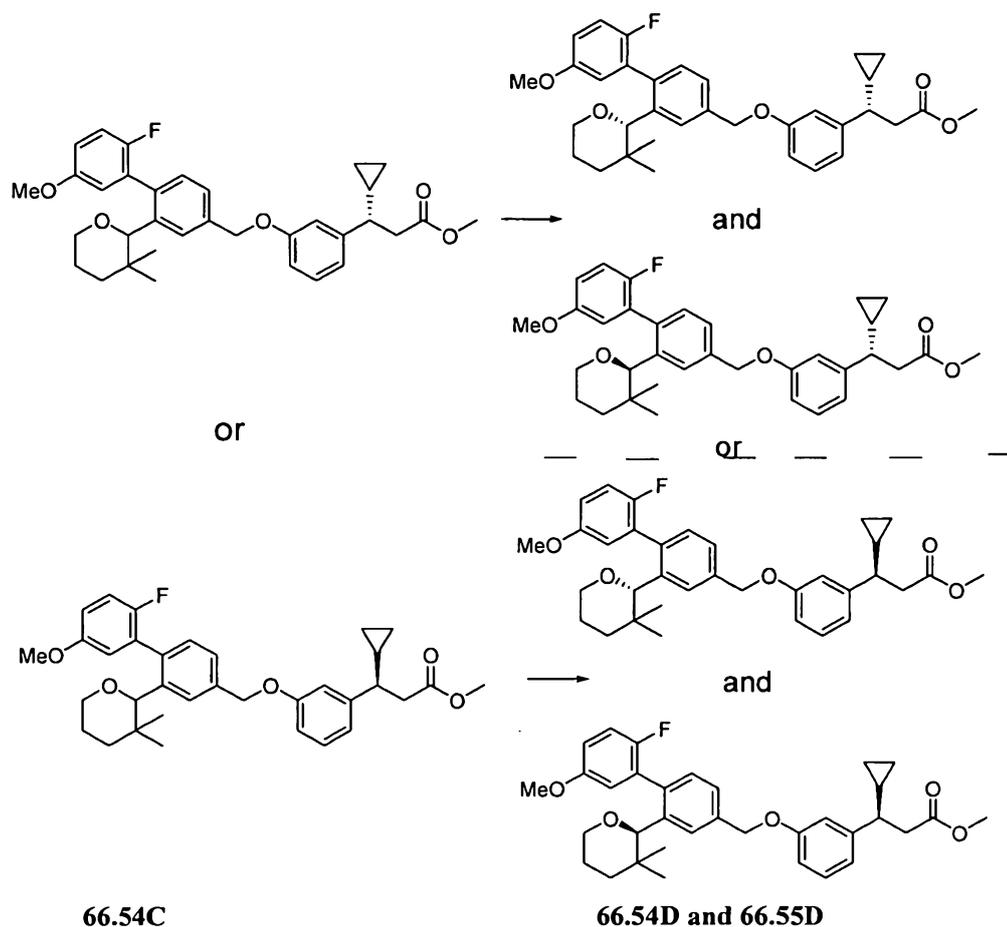
[0824] **Example 66.54 and 66.55**



[0825] **Methyl (3S)-3-cyclopropyl-3-(3-(((2'-fluoro-2-(2-hydroxy-3,3-dimethyltetrahydro-2H-pyran-2-yl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2'-fluoro-2-(2-hydroxy-3,3-dimethyltetrahydro-2H-pyran-2-yl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.54B).** To a solution of **66.54A** (see Example 14) (120 mg, 0.227 mmol) in DCM/MeOH (1.5 mL/10 mL) at -78°C , was bubbled O_3 (109 mg, 2.27 mmol) for 10 minutes until the deep blue color did not change. Nitrogen was then bubbled into the solution for 10 minutes. NaBH_4 (25.8 mg, 0.681 mmol) was added, and the mixture was warmed to room temperature and stirred for 16 hours. Additional NaBH_4 (25.8 mg, 0.681 mmol) was added to the reaction, and LC-MS indicated that the reaction was complete. The solvent was removed and the residue was diluted with EtOAc and washed with saturated NaHCO_3 , water, and brine. The organic layer was then dried, evaporated, and the product was used in the next step without further purification. ^1H NMR (500 MHz, CDCl_3) δ ppm 7.35 (1 H, d, $J=1.5$ Hz), 7.27 (1 H, dd, $J=7.9, 1.8$ Hz), 7.09-7.18 (2 H, m), 6.88 (1 H, t, $J=9.0$ Hz), 6.56 - 6.78 (5 H, m), 4.97 (2 H, s), 3.56 - 3.73 (3 H, m), 3.46 (3 H, s), 3.46 (1 H, d, $J=6.8$ Hz), 2.50 - 2.69 (2 H, m), 2.21 (1 H, m), 1.32 (2 H, br. s.), 1.33 (1 H, dd, $J=7.6, 5.1$ Hz), 1.08 - 1.27 (2 H, m), 0.69 - 0.91 (7 H, m), 0.36 - 0.59 (1 H, m), 0.22 - 0.34 (1 H, m), 0.11 (1 H, dt, $J=9.7, 4.8$ Hz), -0.09 - 0.05 (1 H, m).



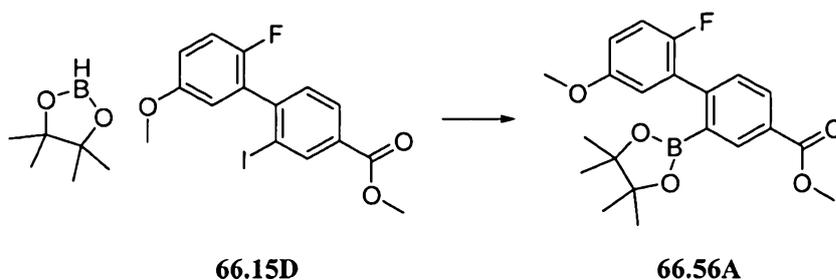
[0826] **Methyl (3S)-3-cyclopropyl-3-(3-(((2-(3,3-dimethyltetrahydro-2H-pyran-2-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2-(3,3-dimethyltetrahydro-2H-pyran-2-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.54C).** To a solution 66.54B (128 mg, 0.227 mmol) in 15 mL DCM at -78°C was added TFA (169 μ L, 2.275 mmol). The resulting mixture was stirred for 15 minutes and then triethylsilane (363 μ L, 2.275 mmol) was added. The mixture was slowly returned to room temperature over 1 hour. The product was chromatographed on silica gel (hexane:EtOAc 5:1 R_f=0.2) to give product. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.47 (1 H, dd, J=14.1, 2.0 Hz), 7.26 (1 H, ddd, J=12.7, 8.0, 2.3 Hz), 6.97 - 7.17 (2 H, m), 6.80 - 6.97 (1 H, m), 6.48 - 6.78 (5H, m), 4.95 (2 H, s), 3.99-4.07(1H, m), 3.64 (3 H, d, J=3.1 Hz), 3.46 (3 H, s), 3.30-3.35 (1 H, dd, J=11.5, 2.5 Hz), 2.52 - 2.71 (2 H, m), 2.20 (1 H, ddd, J=10.0, 7.6, 7.4 Hz), 1.05 - 1.34 (4 H, m), 0.66 - 0.94 (4 H, m), 0.41 (1 H, m), 0.34 - 0.59 (1 H, m), 0.23-0.26 (1H, m), 0.17-0.23 (3 H, m), 0.05 - 0.15 (1 H, m), -0.01-0.08 (1 H, m). Mass Spectrum (ESI) m/e = 564.0 [M+18].



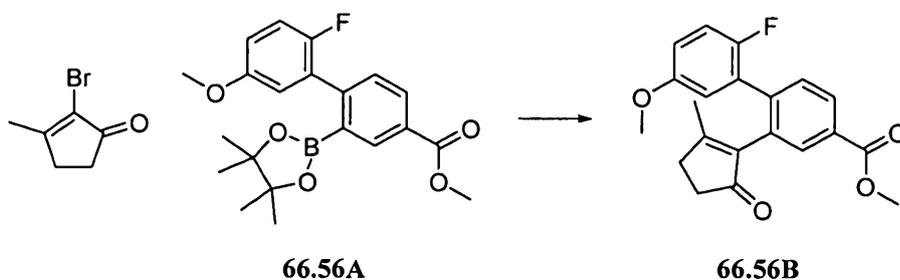
[0827] Methyl (3S)-3-cyclopropyl-3-(3-(((2-(2S)-3,3-dimethyltetrahydro-2H-pyran-2-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate and methyl (3S)-3-cyclopropyl-3-(3-(((2-(2R)-3,3-dimethyltetrahydro-2H-pyran-2-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate; or methyl (3R)-3-cyclopropyl-3-(3-(((2-(2S)-3,3-dimethyltetrahydro-2H-pyran-2-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate and methyl (3R)-3-cyclopropyl-3-(3-(((2-(2R)-3,3-dimethyltetrahydro-2H-pyran-2-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.54D and 66.55D). Compounds 66.54D and 66.55D were separated by chiral HPLC using an OD-H column with isocratic 4% isopropanol in hexane. The first eluted enantiomer was 66.54D. Mass Spectrum (ESI) $m/e = 564.0.0$ [M+18]. The second eluted enantiomer was 66.55D.

Hz), 1.70 - 1.85 (1 H, m), 1.06 - 1.34 (3 H, m), 0.84 - 0.95 (1 H, m, J=8.9, 8.9, 4.3, 4.1 Hz), 0.74 (3 H, d, J=2.7 Hz), 0.42 (1 H, tt, J=8.8, 4.7 Hz), 0.16 - 0.33 (4 H, m), 0.06 - 0.15 (1 H, m, J=9.5, 5.1, 4.8, 4.8 Hz), -0.04 - 0.04 (1 H, m). Example 66.55 was synthesized using 66.55D in place of 66.54D. Mass Spectrum (ESI) m/e = 533.2 [M+1].

[0829] **Example 66.56**

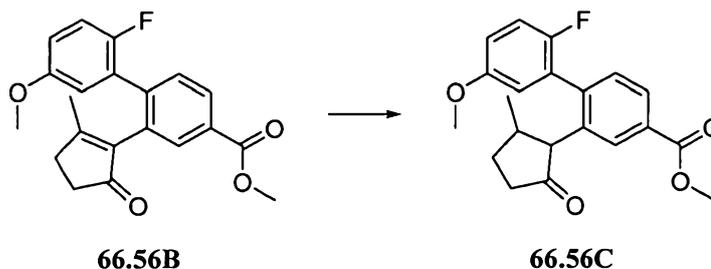


[0830] **Methyl 2'-fluoro-5'-(methoxy)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,1'-biphenyl-4-carboxylate (66.56A)**. A screw-cap vial was charged with 66.15D (2.08 g, 5.39 mmol), 1,4-dioxane (20 mL), and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) DCM adduct (available from Strem) (0.220 g, 0.269 mmol). The suspension was sparged with N₂, and to it were added TEA (2.25 mL, 16.2 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (available from Aldrich) (1.17 mL, 8.08 mmol). The resulting mixture was stirred overnight at 100 °C (sealed vial), cooled to room temperature, diluted with water, and extracted with EtOAc. The combined organic layers were washed with water, 1 N HCl, and brine, dried (MgSO₄), and concentrated. The crude product was twice purified by silica gel flash chromatography (0-15% EtOAc/hexane) to afford 66.56A (1.09 g, 52% yield) as a crystalline white solid.

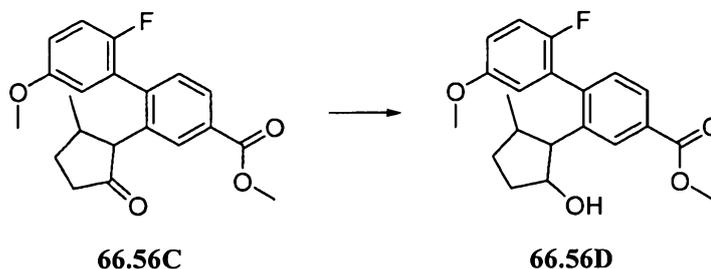


[0831] **Methyl 2'-fluoro-2-(2-methyl-5-oxo-1-cyclopenten-1-yl)-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.56B)**. A screw-cap vial was charged with 2-bromo-3-methyl-2-cyclopenten-1-one (available from Aldrich) (0.68 g, 3.9 mmol),

66.56A (1.00 g, 2.6 mmol), potassium phosphate (1.6 g, 7.8 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (available from Aldrich) (0.33 g, 0.80 mmol), palladium(II) acetate (available from Aldrich) (0.058 g, 0.26 mmol), degassed THF (17 mL), and water (0.23 mL, 13 mmol). The mixture was purged three times with N₂, stirred for 48 hours at room temperature under N₂, filtered through silica gel (EtOAc), and concentrated. Trituration of the crude residue with ether afforded **66.56B** (0.72 g, 78% yield) as a pale yellow solid.

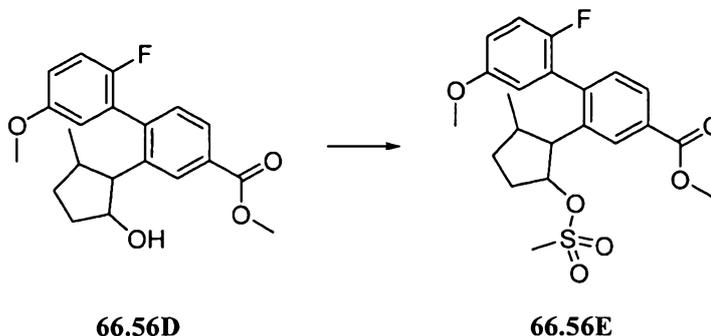


[0832] **Methyl 2'-fluoro-2-(2-methyl-5-oxocyclopentyl)-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.56C)**. A pressure tube was charged with **66.56B** (0.72 g, 2.0 mmol), EtOAc (20 mL), and Pd/C (10 wt. %) (0.22 g, 0.20 mmol). The tube was purged three times with H₂ at 45 psi and sealed, and the contents were stirred for 48 hours. The mixture was filtered through silica gel (EtOAc) and concentrated. The crude product was purified by silica gel flash chromatography (0-20% EtOAc/hexane) to afford **66.56C** (mixture of diastereomers) (0.63 g, 87% yield) as a colorless oil.

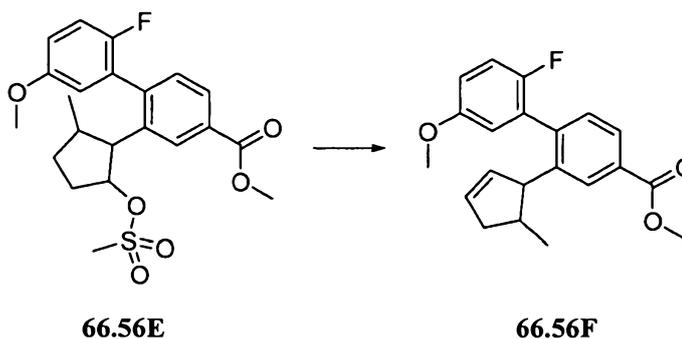


[0833] **Methyl 2'-fluoro-2-(2-hydroxy-5-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.56D)**. A 100 mL round bottom flask was charged with **66.56C** (mixture of diastereomers) (0.59 g, 1.7 mmol) and 1:1 THF/MeOH (15 mL). To the solution was added sodium borohydride (0.063 g, 1.7 mmol) in one portion at room temperature. The mixture was stirred for 1 hour, quenched with 1 N HCl, and extracted with ether. The combined organic layers were dried (MgSO₄) and concentrated to afford **66.56D** (mixture of diastereomers) as a colorless oil. The product thus obtained was used

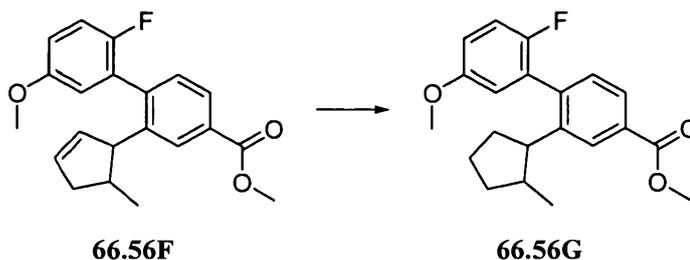
without further purification.



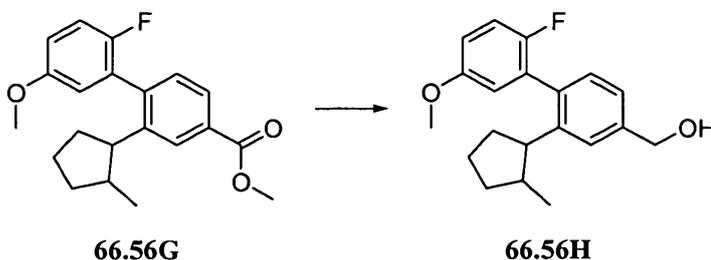
[0834] Methyl 2'-fluoro-2-(2-methyl-5-((methylsulfonyl)oxy)cyclopentyl)-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.56E). A 250 mL round bottom flask was charged with **66.56D** (mixture of diastereomers) (0.61 g, 1.7 mmol), DCM (10 mL), and TEA (0.28 mL, 2.0 mmol) and cooled to 0 °C. To the cold solution was added methanesulfonyl chloride (available from Aldrich) (0.16 mL, 2.0 mmol) dropwise. The cooling bath was removed, and the mixture was stirred for 1 hour at ambient temperature. The mixture was diluted with EtOAc, washed with water and brine, dried (MgSO₄), and concentrated. The crude product was purified by silica gel flash chromatography (0-40% EtOAc/hexane) to afford **66.56E** (mixture of diastereomers) (0.69 g, 93% yield) as a colorless oil.



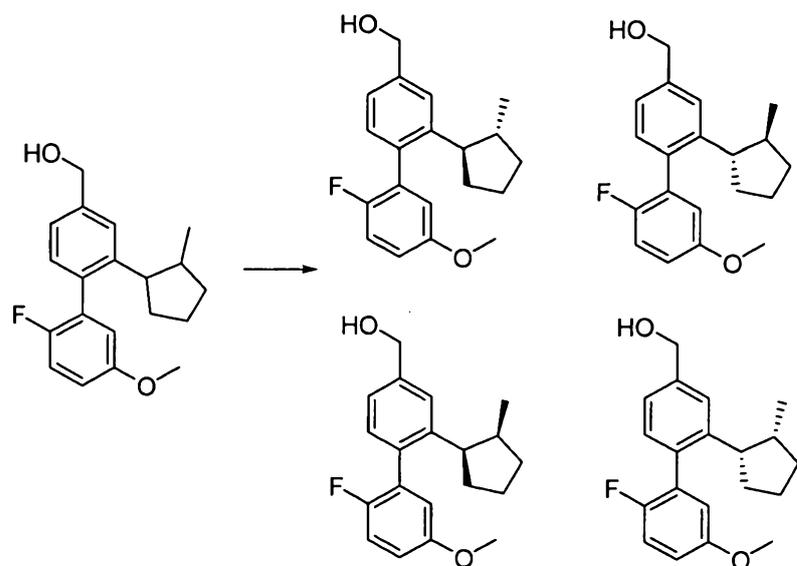
[0835] Methyl 2'-fluoro-2-(5-methyl-2-cyclopenten-1-yl)-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.56F). A 200 mL round bottom flask was charged with **66.56E** (mixture of diastereomers) (0.59 g, 1.4 mmol), toluene (10 mL), and DBU (2.0 mL, 14 mmol). The resulting solution was stirred for 16 hours at 95°C, cooled to room temperature, and quenched with 1 N HCl. The mixture was diluted with EtOAc, washed with water and brine, dried (MgSO₄), and concentrated. The initial product was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to afford **66.56F** (mixture of diastereomers) (0.31 g, 67% yield) as a colorless oil.



[0836] Methyl 2'-fluoro-2-(2-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.56G). A 100 mL round bottom flask was charged with **66.56F** (mixture of diastereomers) (0.31 g, 0.91 mmol), EtOAc (10 mL), and Pd/C (10 wt. %) (0.097 g, 0.091 mmol). The mixture was purged three times with H₂, stirred overnight under a H₂ balloon, filtered through silica gel (EtOAc), and concentrated to afford **66.56G** (mixture of diastereomers) (0.31 g, 99% yield) as a colorless oil.



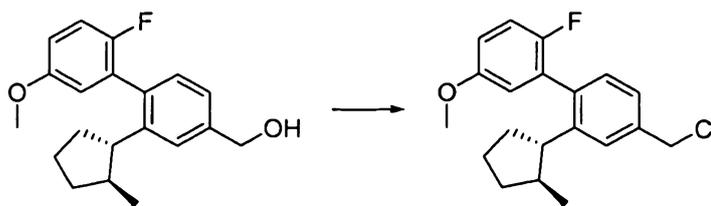
[0837] (2'-Fluoro-2-(2-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (66.56H). A 200 mL round bottom flask was charged with **66.56G** (0.31 g, 0.91 mmol) and THF (10 mL). To the solution was added LAH (1.0 M in THF) (0.91 mL, 0.91 mmol) dropwise at room temperature. The resulting solution was stirred for 15 minutes, quenched with saturated aqueous Rochelle salt, and extracted with ether. The combined organic layers were dried (MgSO₄) and concentrated. The initial product was purified by silica gel flash chromatography (0-30% EtOAc/hexane) to afford **66.56H** (mixture of diastereomers) (0.27 g, 95% yield) as a colorless oil.



66.56H

66.56I and 66.56J and 66.56K and 66.56L

[0838] (2'-Fluoro-2-((1R,2R)-2-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol and (2'-fluoro-2-((1R,2S)-2-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol and (2'-fluoro-2-((1S,2S)-2-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol and (2'-fluoro-2-((1S,2R)-2-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (66.56I, 66.56J, 66.56K, and 66.56L). 66.56H (0.27 g, 0.86 mmol) was resolved by chiral HPLC (Chiralcel OD column, 2% IPA/hexane, detection at 220 nm) to afford (in order of elution) an epimeric mixture of 66.56I and 66.56J, 66.56K (0.11 g, 41% yield), and 66.56L (0.030 g, 11% yield) as colorless oils. The epimeric mixture of 66.56I and 66.56J was resolved by chiral HPLC (Chiralpak AD column, 2% IPA/hexane, detection at 220 nm) to afford (in order of elution) 66.56I (0.11 g, 41% yield) and 66.56J (0.028 g, 10% yield) as colorless oils.



66.56K

66.56M

Only one of the stereoisomers is shown above, but it could be any of the four.

[0839] 4-(Chloromethyl)-2'-fluoro-2-((1S,2S)-2-methylcyclopentyl)-5'-

(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2'-fluoro-2-((1R,2R)-2-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2'-fluoro-2-((1R,2S)-2-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2'-fluoro-2-((1S,2R)-2-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl (66.56M). A 25 mL conical flask was charged with 66.56K (0.12 g, 0.38 mmol) and DCM (3 mL). To the solution were added thionyl chloride (available from Aldrich) (0.056 mL, 0.76 mmol) and catalytic DMF (one drop). The resulting solution was stirred overnight at room temperature and concentrated. The crude product was purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford 66.56M (0.093 g, 73%) as a colorless oil.

[0840] (3S)-3-Cyclopropyl-3-(3-(((2'-fluoro-2-((1S,2S)-2-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-Cyclopropyl-3-(3-(((2'-fluoro-2-((1R,2R)-2-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-Cyclopropyl-3-(3-(((2'-fluoro-2-((1R,2S)-2-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-Cyclopropyl-3-(3-(((2'-fluoro-2-((1S,2R)-2-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-Cyclopropyl-3-(3-(((2'-fluoro-2-((1S,2S)-2-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-Cyclopropyl-3-(3-(((2'-fluoro-2-((1R,2R)-2-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-Cyclopropyl-3-(3-(((2'-fluoro-2-((1R,2S)-2-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-Cyclopropyl-3-(3-(((2'-fluoro-2-((1S,2R)-2-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.56). 66.56 was prepared from 66.56M and 8.4 according to the analogous methods described in Example 7. MS ESI (pos.) m/e: 503.2 (M+H)⁺, 520.3 (M+H₂O)⁺, 525.3 (M+Na)⁺.

[0841] Example 66.57

[0842] **Diastereomer of 66.56 (66.57).** Example 66.57 was prepared from the chloromethyl compound derived from 66.56L and 8.4 according to the analogous methods described in Example 66.56. MS ESI (pos.) m/e: 503.2 (M+H)⁺, 520.3 (M+H₂O)⁺, 525.3 (M+Na)⁺.

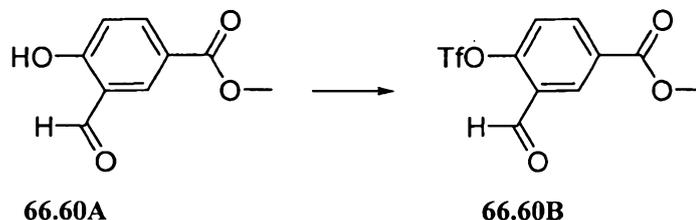
[0843] Example 66.58

[0844] **Diastereomer of 66.56 and 66.57 (66.58).** Example 66.58 was prepared from the chloromethyl compound derived from 66.56I and 8.4 according to the analogous methods described in Example 66.56. MS ESI (pos.) m/e: 503.2 (M+H)⁺, 520.3 (M+H₂O)⁺, 525.3 (M+Na)⁺.

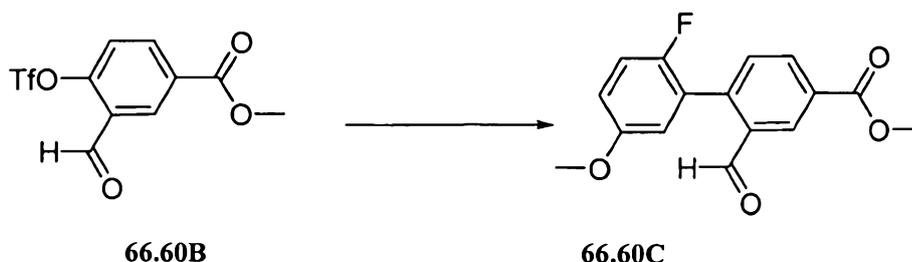
[0845] **Example 66.59**

[0846] **Diastereomer of 66.56, 66.57, and 66.58 (66.59).** Example 66.59 was prepared from the chloromethyl compound derived from 66.56J and 8.4 according to the analogous methods described in Example 66.56. MS ESI (pos.) m/e: 503.2 (M+H)⁺, 520.3 (M+H₂O)⁺, 525.3 (M+Na)⁺.

[0847] **Example 66.60**

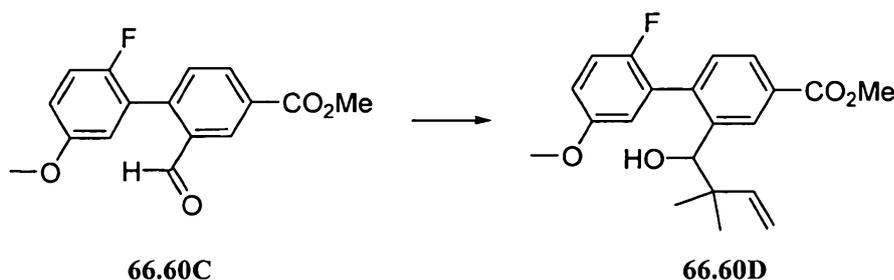


[0848] **Methyl 3-formyl-4-(trifluoromethylsulfonyloxy)benzoate (66.60B).** TEA (6.81 mL, 48.8 mmol), and N,N-dimethylpyridin-4-amine (0.298 g, 2.44 mmol) were added to a solution of methyl 3-formyl-4-hydroxybenzoate (commercially available from Aldrich) (4.40 g, 24.4 mmol) in DCM (26 mL). The resulting mixture was stirred at room temperature for 20 minutes and then N-phenyltrifluoromethanesulfonimide (9.60 g, 26.9 mmol) was added in one portion. The mixture was then stirred at room temperature for 30 minutes. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:1 EtOAc / hexane) and gave 66.60B, a colorless oil, in 99% yield (7.57 g).

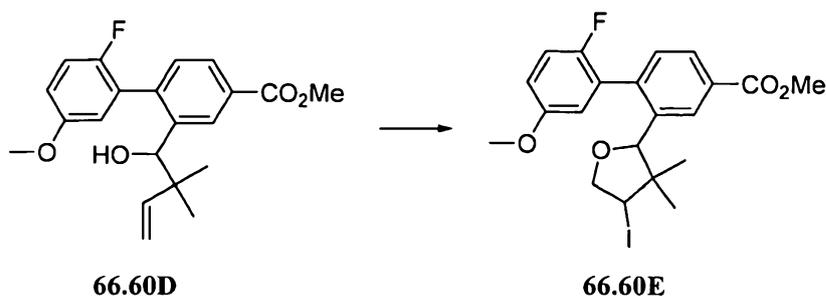


[0849] **Methyl 2'-fluoro-2-formyl-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.60C).** A mixture of methyl 3-formyl-4-(trifluoromethylsulfonyloxy)benzoate (66.60B) (7.57 g, 24.2 mmol), 2-fluoro-5-methoxy-phenylboronic

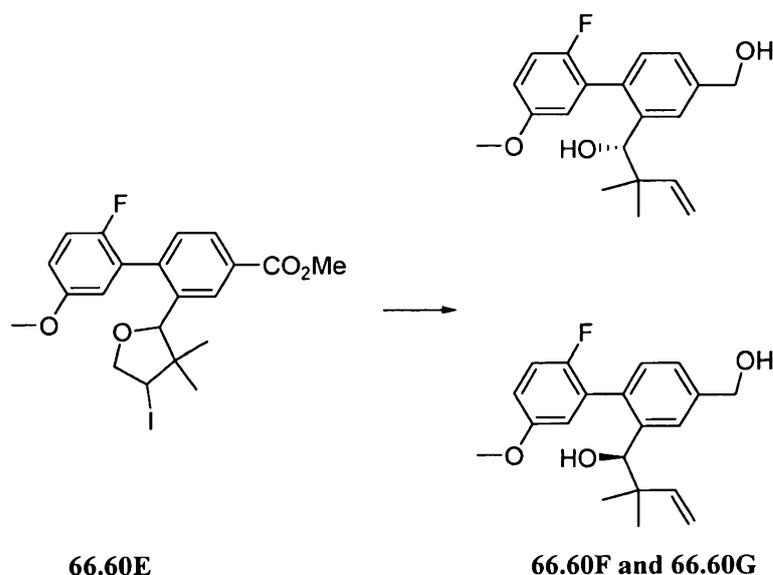
acid (commercially available from Aldrich) (12.4 g, 72.7 mmol), cesium carbonate (27.6 g, 84.9 mmol), and tetrakis(triphenylphosphine) palladium (2.80 g, 2.42 mmol) in 1,2-dimethoxyethane (DME) (75 mL) was degassed with N₂ at room temperature. The mixture was heated at 95°C for 9 hours. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:19 EtOAc / hexane) and gave **66.60C**, a white solid, in 56% yield (2.9 g). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.88 (dd, J = 4Hz, 1H), 8.45 (s, 1H), 8.28 (m, 1H), 7.69 (d, j = 8 Hz, 1H), 7.29 (t, J = 9 HZ, 1H), 7.08 (m, 2H), 3.92 (s, 3H), 3.79 (s, 3H).



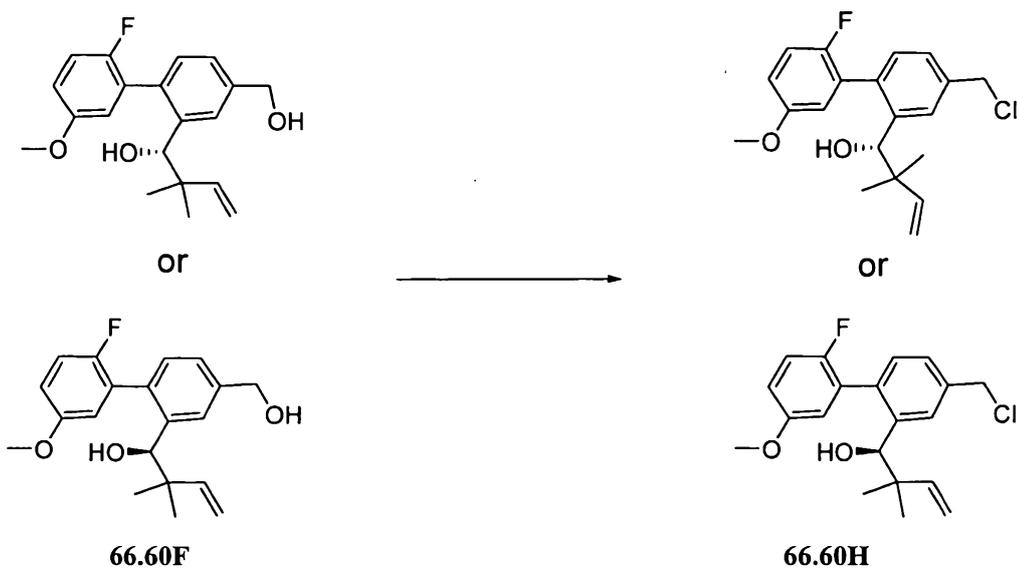
[0850] Methyl 2'-fluoro-2-(1-hydroxy-2,2-dimethyl-3-butenyl)-5'-(methoxy)-1,1'-biphenyl-4-carboxylate(66.60D). To a mixture of **66.60C** (0.38 g, 1.3 mmol), 1-bromo-3-methylbut-2-ene (commercially available from Aldrich) (0.31 mL, 2.6 mmol) and sodium iodide (0.40 g, 2.6 mmol) in DMF(8 mL), was added indium (0.30 g, 2.6 mmol). The resulting mixture was stirred at room temperature for 1 hour and then additional 1-bromo-3-methylbut-2-ene (100 mg) and indium (100 mg) were added and the mixture was stirred at room temperature for one more hour. The reaction was quenched with water (20 mL) and extracted with EtOAc (200 mL). The organic phase was washed with brine, dried over anhydrous sodium sulfate, and filtered. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:4 EtOAc / hexane) and gave product (**66.60D**), in 94% yield.



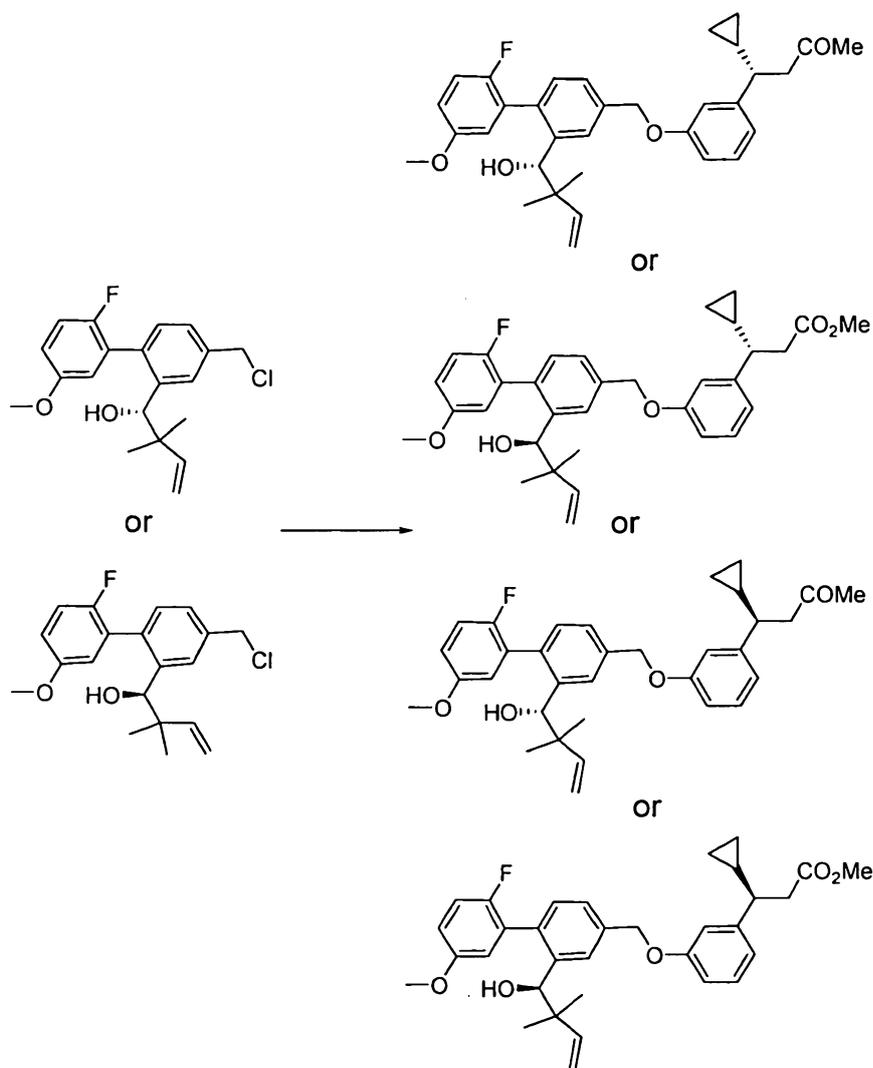
[0851] **Methyl 2'-fluoro-2-(3-iodo-2,2-dimethylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.60E)**. To a mixture of NaHCO₃ (0.035 g, 0.42 mmol) and **66.60D** (0.050 g, 0.14 mmol) in ACN (2 mL), was added iodine (0.12 g, 0.49 mmol). The mixture was then stirred at room temperature for 16 hours. Next, the mixture was poured into a 0.2 M solution of Na₂S₂O₃ and extracted with EtOAc. The organic phase was dried over anhydrous Na₂SO₄ and filtered. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:19 EtOAc / hexane) and gave product **66.60E**, a white solid, in 84% yield.



[0852] **(1S)-1-(2'-Fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-3-buten-1-ol (66.60F)** and **(1R)-1-(2'-fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-3-buten-1-ol (66.60G)**. To a mixture of **66.60E** (0.460 g, 0.950 mmol) in THF (12 mL), was added LAH (0.108 g, 2.85 mmol), and the mixture was stirred at room temperature for 45 minutes. The reaction mixture was then poured into water and extracted with EtOAc. The organic phase was dried over anhydrous Na₂SO₄ and filtered. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:2 EtOAc / hexane) and gave racemic product, which was separated by chiral chromatography (column: OD-H; solvent: 6% i-PrOH/hexane) to yield **66.60F** (72 mg) (retention time = 12.9 min) and **66.60G** (74 mg) (retention time = 18.2 min).



[0853] (1S)-1-(4-(Chloromethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-3-buten-1-ol or (1R)-1-(4-(chloromethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-3-buten-1-ol (**66.60H**). Thionyl chloride (0.27 g, 2.2 mmol) was added to a solution of **66.60F** (0.074 g, 0.22 mmol) in DCM (2 mL), and the mixture was stirred at room temperature for 40 minutes. After removing solvent, **66.60H** was obtained.

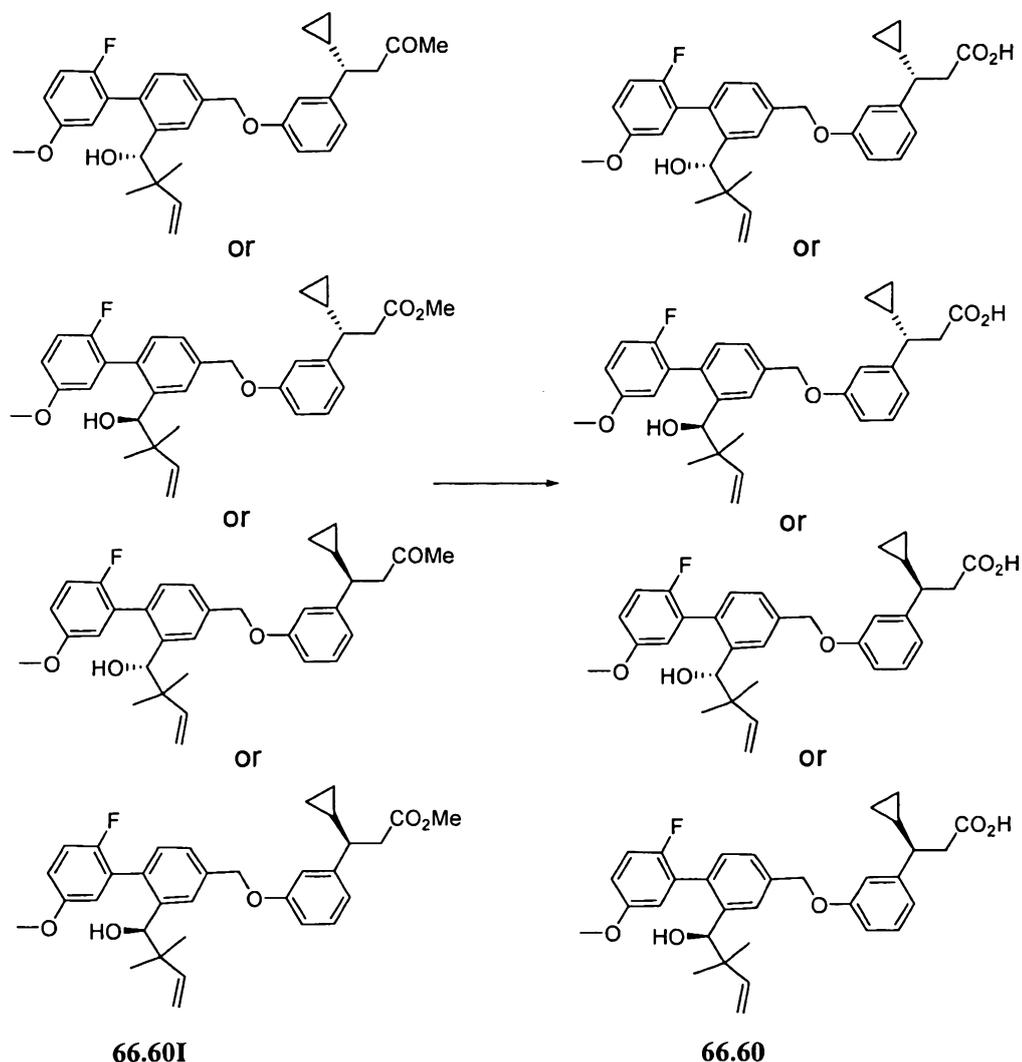


66.60H

66.60I

[0854] (3S)-3-Cyclopropyl-3-(3-(((2'-fluoro-2-((1S)-1-hydroxy-2,2-dimethyl-3-butenyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl) propanoic acid methyl ester or (3S)-3-cyclopropyl-3-(3-(((2'-fluoro-2-((1R)-1-hydroxy-2,2-dimethyl-3-butenyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl) propanoic acid methyl ester or (3R)-3-cyclopropyl-3-(3-(((2'-fluoro-2-((1S)-1-hydroxy-2,2-dimethyl-3-butenyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl) propanoic acid methyl ester or (3R)-3-cyclopropyl-3-(3-(((2'-fluoro-2-((1R)-1-hydroxy-2,2-dimethyl-3-butenyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl) propanoic acid methyl ester (66.60I). A mixture of 8.4 (0.019 g, 0.087 mmol), 66.60H (0.019 g, 0.054 mmol) and Cs₂CO₃ (0.035 g, 0.11 mmol) in DMF (1.5 mL) was stirred at room

temperature overnight. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:6 EtOAc / hexane) and gave **66.60I** (30 mg).

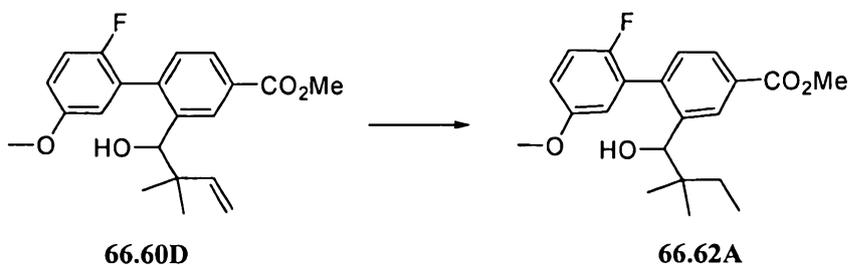


[0855] (3S)-3-Cyclopropyl-3-(3-(((2'-fluoro-2-((1S)-1-hydroxy-2,2-dimethyl-3-butenyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl) propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2'-fluoro-2-((1R)-1-hydroxy-2,2-dimethyl-3-butenyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl) propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2'-fluoro-2-((1S)-1-hydroxy-2,2-dimethyl-3-butenyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl) propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2'-fluoro-2-((1R)-1-hydroxy-2,2-dimethyl-3-butenyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl) propanoic acid (**66.60**). A

mixture of **60.60I** (0.030 g, 0.056 mmol), NaOH(aq, 10%) (0.6 mL) and EtOH (2 mL) was stirred at room temperature for 16 hours. The product was purified by reverse-phase HPLC and **66.60** (7 mg) was obtained. MS ESI (neg.) m/e: 517 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.64 (d, 1H), 7.42 (m, 1H), 7.18-7.23 (m, 2H), 7.03 (m, 1H), 6.76 (m, 1H), 5.78 (m, 1H), 5.16 (s, 2H), 5.03 (m, 2H), 3.81 (m, 3H), 2.64-2.83 (m, 2H), 2.34(m, 1H), 1.27 (m, 1H), 1.05(m, 1H), 0.84 (s, 3H), 0.79 (s, 3H), 0.59 (m, 1H), 0.46 (m, 1H), 0.29 (m, 1H), 0.17 (m, 1H).

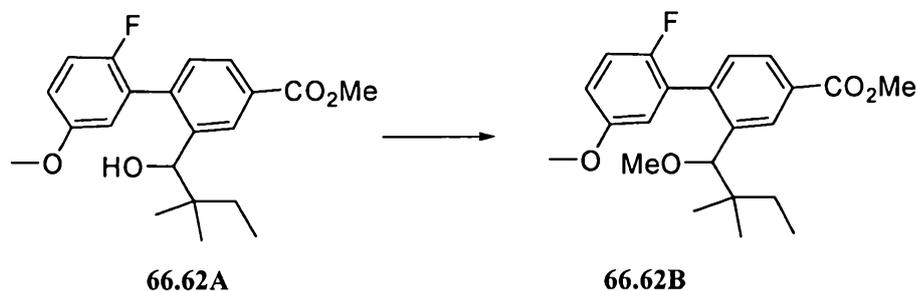
[0856] **(3S)-3-Cyclopropyl-3-(3-(((2'-fluoro-2-((1S)-1-hydroxy-2,2-dimethyl-3-butenyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl) propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2'-fluoro-2-((1R)-1-hydroxy-2,2-dimethyl-3-butenyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl) propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2'-fluoro-2-((1S)-1-hydroxy-2,2-dimethyl-3-butenyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl) propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2'-fluoro-2-((1R)-1-hydroxy-2,2-dimethyl-3-butenyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl) propanoic acid (66.61).** Example **66.61** was prepared from **66.60H** and **8.4** using the alkylation and hydrolysis conditions described with respect to **60.60I**. The product was purified by reverse-phase HPLC and **66.61** (6 mg) was obtained. MS ESI (neg.) m/e: 517 (M-H)⁺. ¹H NMR (400 MHz, CD₃OD) δ ppm 7.40 (d, 1H), 7.33 (m, 1H), 7.10-7.40 (m, 3H), 6.79-6.89 (m, 5H), 5.76 (m, 1H), 5.14 (s, 2H), 4.74 (m, 2H), 3.79 (s, 3H), 2.64-2.77 (m, 2H), 2.32(m, 1H), 1.03 (m, 1H), 0.82 (s, 3H), 0.72 (s, 3H), 0.57 (m, 1H), 0.38 (m, 1H), 0.28 (m, 1H), 0.11 (m, 1H).

[0857] **Example 66.62**

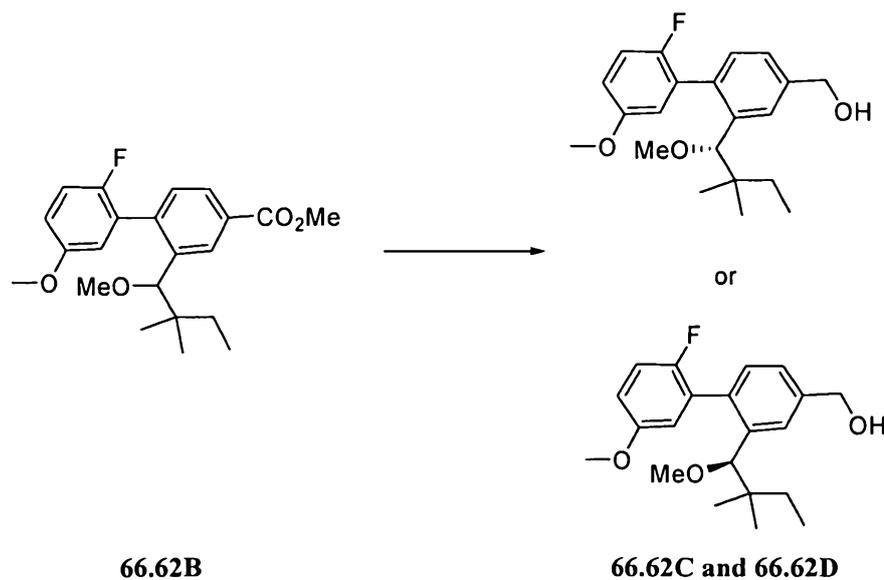


[0858] **Methyl 2'-fluoro-2-(1-hydroxy-2,2-dimethylbutyl)-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.62A).** To a solution of **66.60D** (0.453 g, 1.26 mmol) in MeOH (10 mL)(degassed by N₂), was added palladium on carbon (0.135 g, 1.26 mmol). The resulting mixture was stirred at room temperature under H₂ for 18 hrs. The reaction

mixture was then filtered through silica gel. After removing solvent, **66.62A** (394mg) was obtained as a colorless oil.

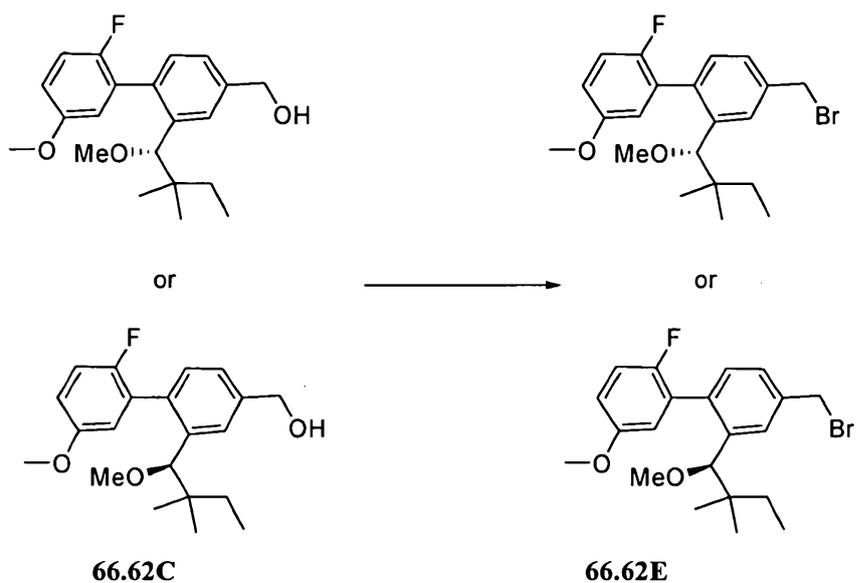


[0859] **Methyl 2-(2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.62B)**. To a solution of **66.62A** (0.39 g, 1.1 mmol) in DMF (5 mL), was added NaH (0.034 g, 1.4 mmol). The mixture was stirred at room temperature for 10 minutes and then iodomethane (0.20 mL, 3.2 mmol) was added. The mixture was stirred at room temperature for 60 minutes and then it was diluted with EtOAc, washed with water and brine, and dried over anhydrous Na₂SO₄. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:9 EtOAc / hexane) and gave **66.62B**, colorless oil, in 64% yield (260mg).

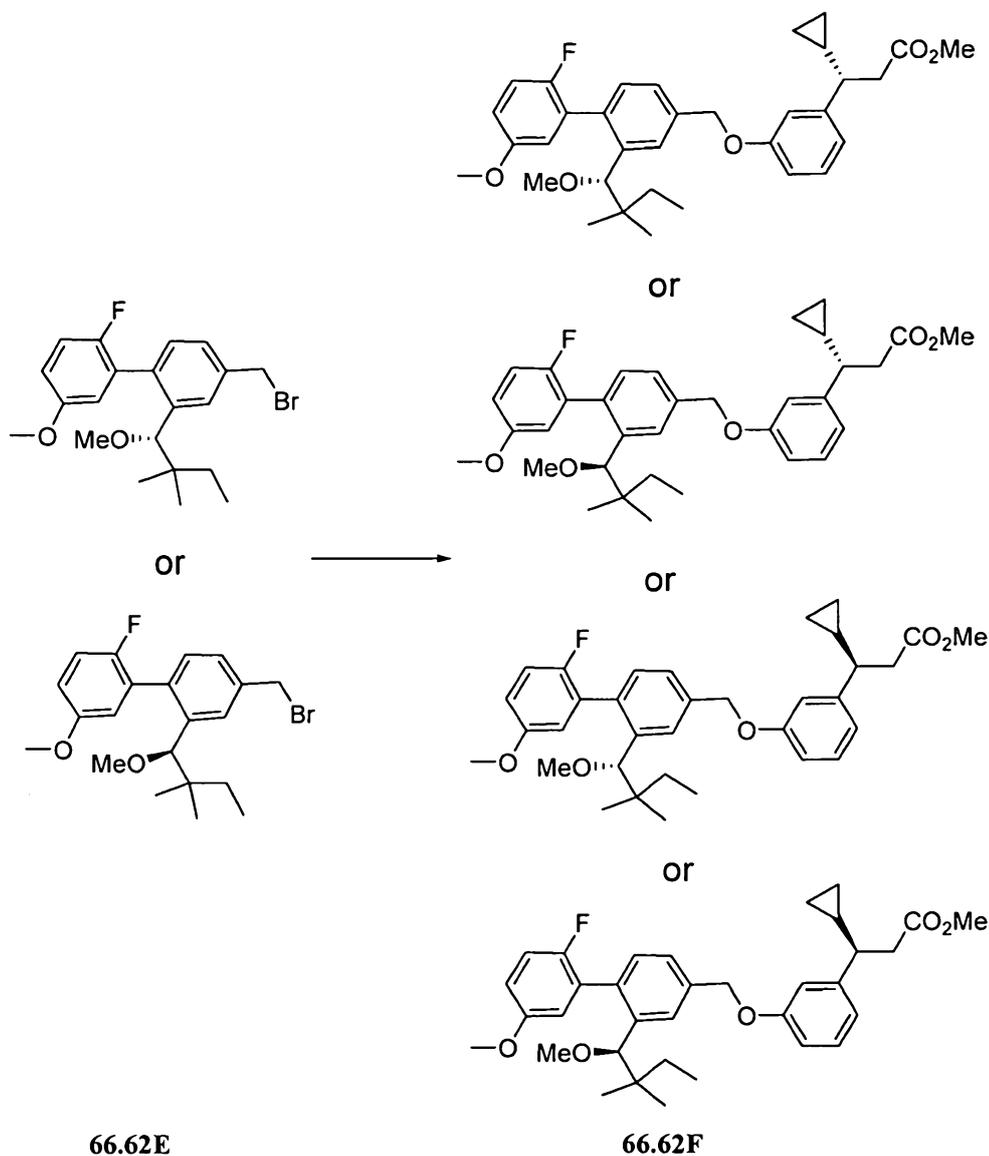


[0860] **(2-((1S)-2,2-Dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol and (2-((1R)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (66.62C and 66.62D)**. To a solution of **66.62B** (0.26 g, 0.69 mmol) in THF (4 mL), was added LAH (0.026 g, 0.69

mmol). The resulting mixture was stirred at room temperature for 10 minutes and then was poured into water and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4 . After removing solvent, the residue was purified by flash chromatography (silica gel, 1:6 EtOAc / hexane) and gave racemic product (157 mg) as a colorless oil, which was separated by chiral chromatography (column: OD; solvent: 6% *i*-PrOH / hexane) to yield **66.62C** (68 mg) (retention time = 11.8 min) and **66.62D** (70 mg) (retention time = 15.1 min).

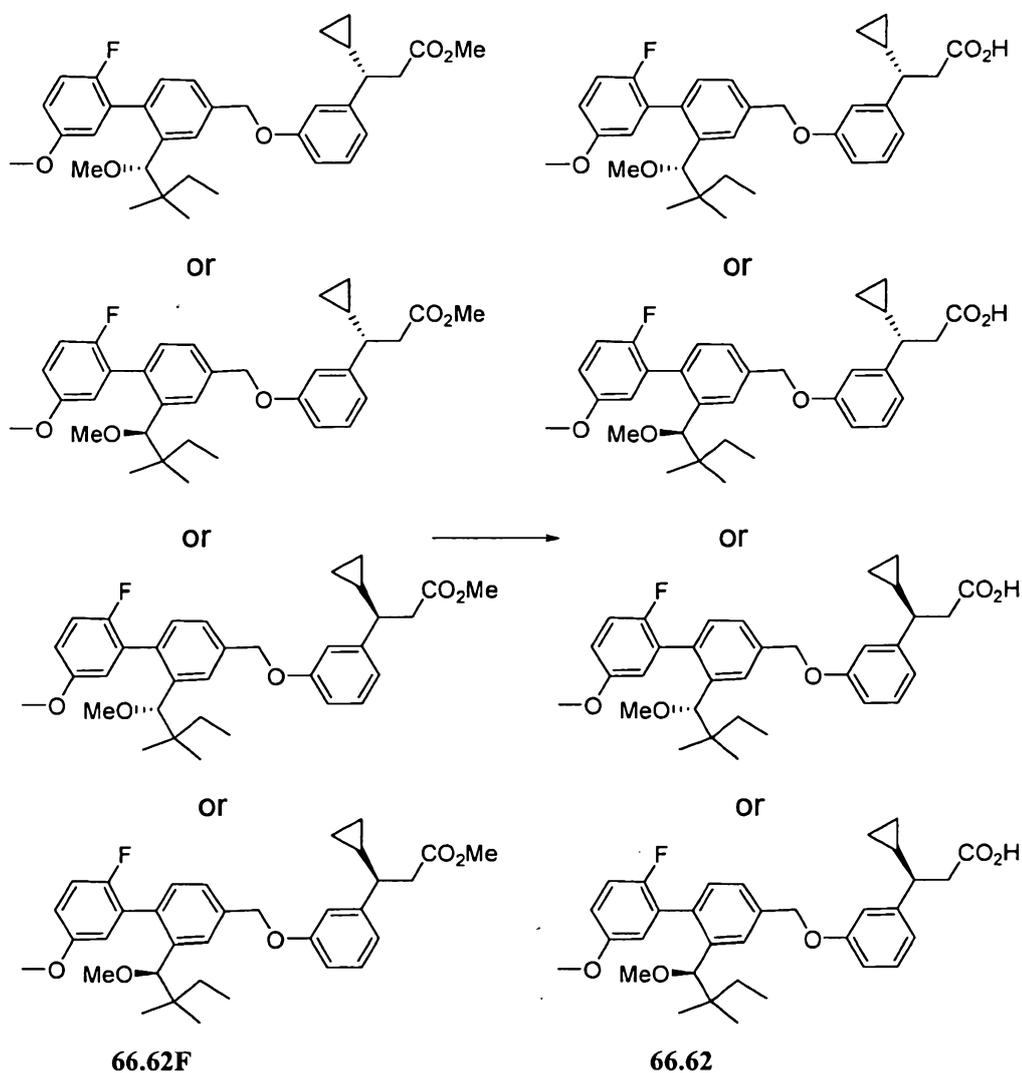


[0861] **4-(Bromomethyl)-2-((1S)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl or 4-(bromomethyl)-2-((1R)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (66.62E)**. To a solution of **66.62C** (0.070 g, 0.20 mmol) in THF (2 mL), was added triphenylphosphine (0.11 g, 0.40 mmol) and 1-bromopyrrolidine-2,5-dione (0.072 g, 0.40 mmol). The resulting mixture was stirred at room temperature for 10 minutes. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:6 EtOAc / hexane) and gave **66.62E** (73 mg).



[0862] Methyl (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3S)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.62F). A mixture of 8.4 (0.018 g, 0.082 mmol),

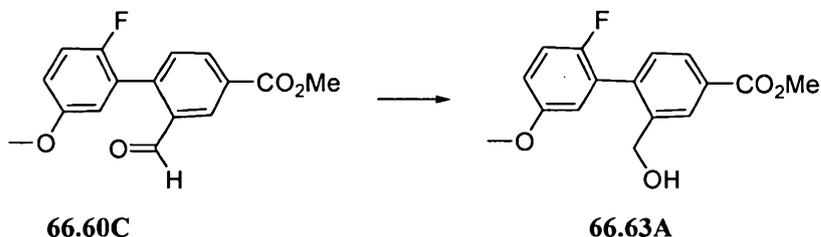
66.62E (0.024 g, 0.059 mmol) and Cs_2CO_3 (0.038 g, 0.12 mmol) in DMF (2 mL) were stirred at room temperature for 2 hours. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:6 EtOAc/hexane) and gave **66.62F** (25mg).



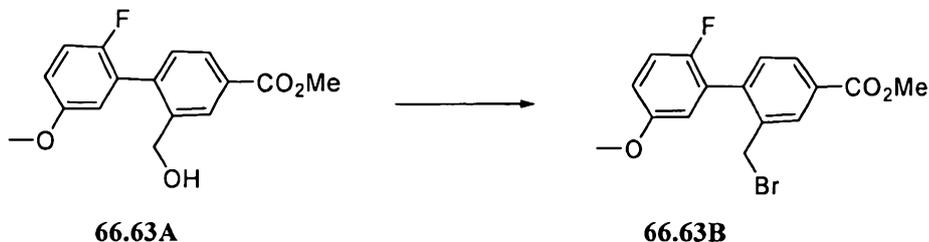
[0863] (3S)-3-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid

(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (**66.62**). A mixture of **66.62F** (0.025 g, 0.044 mmol), NaOH(aq, 10%) (1 mL) and EtOH (3 mL) was stirred at room temperature for 2.5 hours. After removing solvent, the mixture was acidified with 1N HCl to pH3-5 and extracted with EtOAc (120 mL). The organic phase was washed with brine and dried over anhydrous sodium sulfate. After filtering and removing solvent, the residue was purified by flash chromatography (silica gel, 1:6 MeOH / DCM) and gave **66.62** (6.4mg). MS ESI (neg.) m/e: 533 (M-H)⁻. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.57 (m, 1H), 7.43 (m, 1H), 7.08-7.23 (m, 2H), 7.05 (m, 1H), 6.84-6.90 (m, 4H), 6.75 (m, 1H), 5.16 (s, 2H), 4.06-4.29 (m, 1H), 3.80 (s, 3H), 3.23-3.29 (m, 3H), 2.78-2.80 (m, 2H), 2.37(m, 1H), 1.27 (m, 2H), 1.07 (m, 2H), 1.03 (m, 1H), 0.71 (s, 3H), 0.60 (m, 3H), 0.49 (m, 3H), 0.44 (m, 1H), 0.30 (m, 1H), 0.18 (m, 1H).

[0864] **Example 66.63**

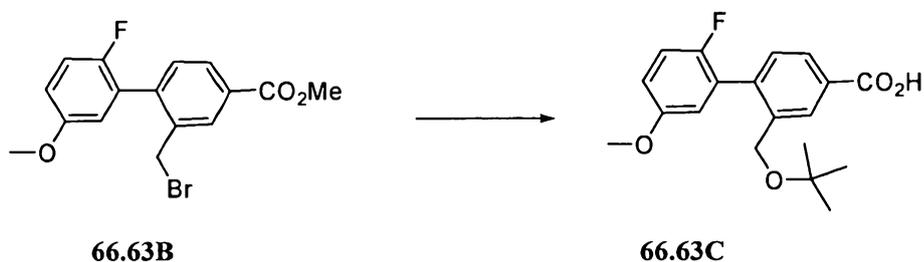


[0865] **Methyl 2'-fluoro-2-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.63A)**. Sodium tetrahydroborate (available from Aldrich) (0.656 g, 17.3 mmol) was added portion by portion slowly to **66.60C** (1.00 g, 3.47 mmol) in MeOH (20 mL). The resulting mixture was stirred at room temperature for 25 minutes. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:2 EtOAc / hexane) and gave **60.63A** (725mg) in 72% yield.

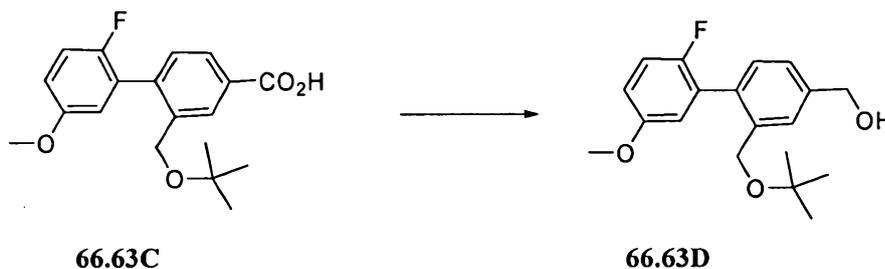


[0866] **Methyl 2-(bromomethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.63B)**. To a solution of **66.63A** (0.725 g, 2.50 mmol) and triphenylphosphine (2.62 g, 9.99 mmol) in THF (20 mL) was added portion by portion 1-bromopyrrolidine-2,5-dione (available from Aldrich) (1.78 g, 9.99 mmol). The resulting

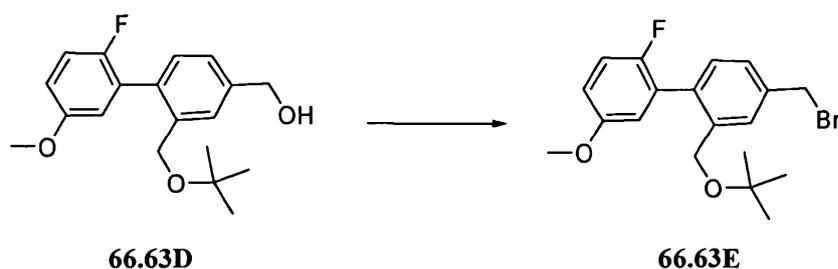
mixture was stirred at room temperature for 20 minutes. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:9 EtOAc / hexane) and gave **60.63B** (882mg) in 100% yield.



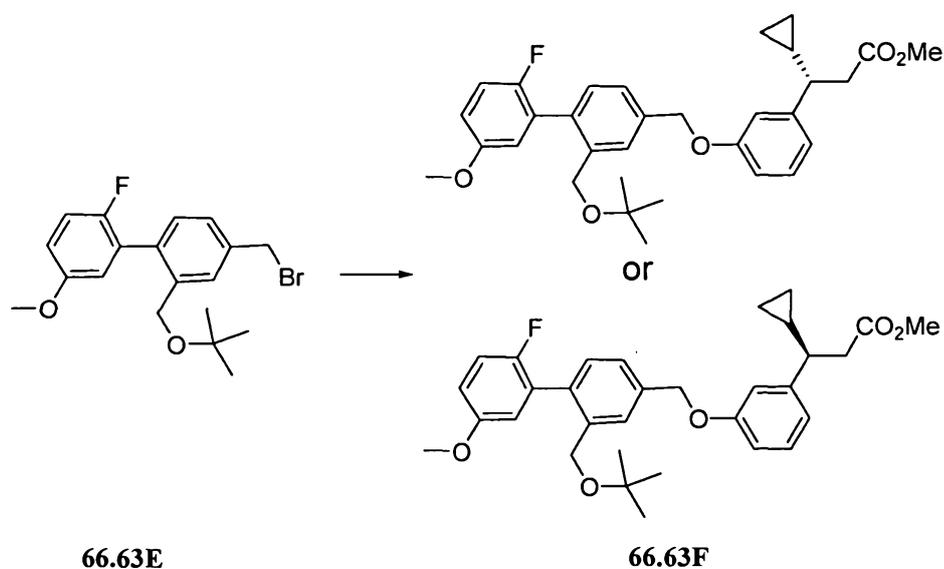
[0867] **2-(((1,1-Dimethylethyl)oxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylic acid (66.63C)**. A mixture of **66.63B** (0.245 g, 0.69 mmol) and sodium 2-methylpropan-2-olate (0.20 g, 2.1 mmol) in DMF (6 mL) was stirred at room temperature for 28 minutes. The mixture was acidified with 1N HCl to pH 3-4 and then was extracted with EtOAc (100 mL). The organic phase was washed with brine and dried over anhydrous Na₂SO₄. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:4 EtOAc / hexane) and gave **60.63B** (49mg) in 20% yield.



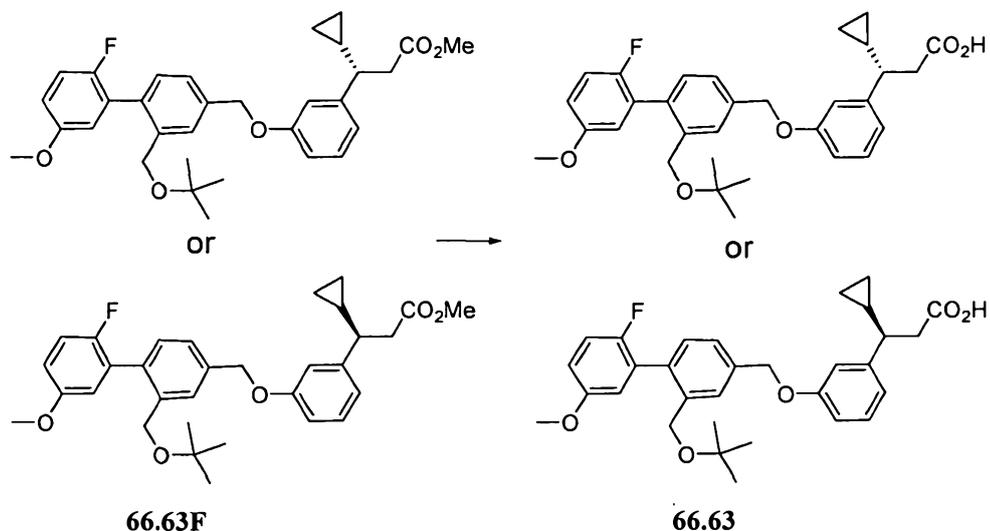
[0868] **(2-(((1,1-Dimethylethyl)oxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (66.63D)**. LAH (0.15 mL, 0.15 mmol) was added to a solution of **66.63C** (0.049 g, 0.15 mmol) in THF (2 mL). The resulting mixture was stirred at room temperature for 10 minutes and then was poured slowly into brine (5 mL). The mixture was extracted with EtOAc (2 x 50 mL). The organic phase was dried over anhydrous sodium sulfate. After filtering and removing solvent, the residue was purified by flash chromatography (silica gel, 1:2 EtOAc / hexane) and gave **60.63D** (6 mg).



[0869] 4-(Bromomethyl)-2-(((1,1-dimethylethyl)oxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (**66.63E**). Bromomethyl compound **66.63E** was prepared using an analogous procedure to that set forth for the synthesis of **66.63B**.

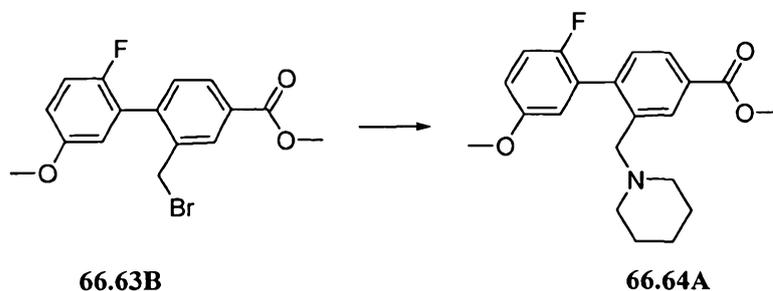


[0870] Methyl (3S)-3-cyclopropyl-3-(3-(((2-(((1,1-dimethylethyl)oxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2-(((1,1-dimethylethyl)oxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (**66.63F**). A mixture of **8.4** (0.0046 g, 0.021 mmol), **66.63E** (0.0061 g, 0.016 mmol) and Cs₂CO₃ (0.010 g, 0.032 mmol) in DMF (1 mL) was stirred at room temperature for 3 hours. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:4 EtOAc / hexane) and gave **60.63F** (6 mg).



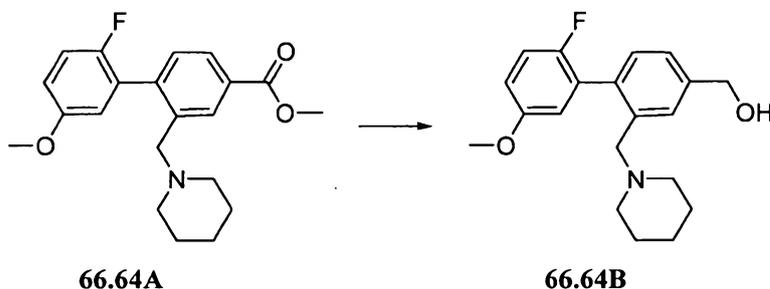
[0871] (3S)-3-Cyclopropyl-3-(3-(((2-(((1,1-dimethylethyl)oxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-(((1,1-dimethylethyl)oxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (**66.63**). **66.63F** was converted to **66.63** using a procedure analogous to that used in **66.62**. MS ESI (neg.) m/e: 505 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.53 (s, 1H), 7.40 (d, 1H), 7.23-7.24 (m, 2H), 7.03 (m, 1H), 6.84-6.92 (m, 4H), 6.79 (m, 1H), 5.18 (m, 2H), 4.33 (m, 2H), 3.79 (s, 3H), 2.73 (m, 1H), 2.60 (m, 1H), 2.31 (m, 1H), 1.20 (m, 1H), 1.10 (s, 9H), 0.90 (m, 1H), 0.60 (m, 1H), 0.49 (m, 1H), 0.34 (m, 1H), 0.20 (m, 1H).

[0872] **Example 66.64**

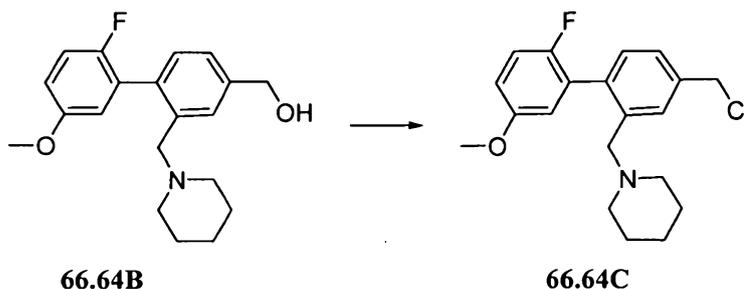


[0873] Methyl 2'-fluoro-5'-(methoxy)-2-(1-piperidinylmethyl)-1,1'-biphenyl-4-carboxylate (**66.64A**). Piperidine (commercially available from Aldrich)(0.038 g, 0.44 mmol) was added to a solution of **66.63B** (0.13 g, 0.37 mmol) in DMSO (3 mL). Cs₂CO₃ (0.18 g, 0.55 mmol) was then added to the reaction and it was stirred at room temperature for 1 hour. EtOAc (100 mL) was added and the organic phase

was washed with water and brine and dried over anhydrous sodium sulfate. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:1 EtOAc/DCM) and gave **66.64A** (100mg) in 76% yield. MS ESI (pos.) m/e: 358 (M+H)⁺.



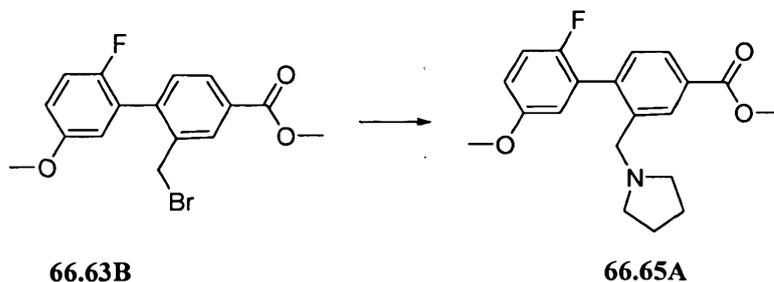
[0874] **(2'-Fluoro-5'-(methoxy)-2-(1-piperidinylmethyl)-1,1'-biphenyl-4-yl)methanol (66.64B)**. LAH (1.0 M solution in THF) (0.55 mL, 0.55 mmol) was added to a solution of **66.64A** (0.098 g, 0.27 mmol) in THF (5 mL). The resulting mixture was stirred at room temperature for 1 hour and then it was diluted with EtOAc, washed with water and brine, and dried over anhydrous Na₂SO₄. After removing solvent, **66.64B** was obtained as a colorless oil in 100% yield.



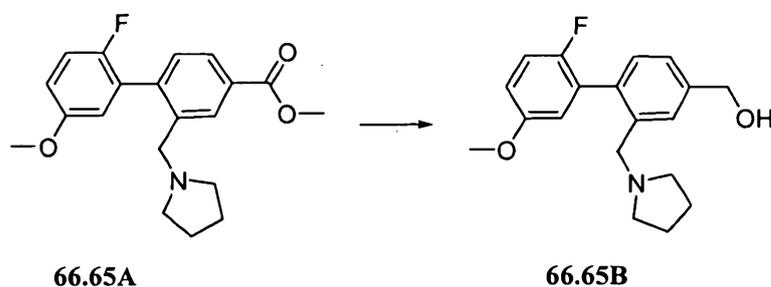
[0875] **1-((4-(Chloromethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)methyl)piperidine (66.64C)**. Thionyl chloride (0.066 g, 0.56 mmol) was added to a solution of **66.64B** (0.023 g, 0.070 mmol) in DCM (1 mL). The resulting mixture was stirred at room temperature for 2 hours. After removing solvent, **66.64C** was obtained in 100% yield.

cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-(1-piperidinylmethyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.64). A mixture of 66.64D (0.039 g, 0.073 mmol), NaOH (aq, 10%) (0.6 mL) and EtOH (2 mL) was stirred at room temperature overnight. The resulting product was purified by reverse phase HPLC. After removing solvent, 66.64 (TFA salt), was obtained (26 mg). MS ESI (neg.) m/e: 516 (M-H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.20(m, 1H), 7.87 (s, 1H), 7.64 (d, 1H), 7.40 (d, 1H), 7.21-7.31 (m, 2H), 7.07 (m, 1H), 6.86-6.96 (m, 4H), 5.19 (s, 2H), 4.04-4.40 (m, 2H), 3.10-3.31 (m, 2H), 2.66 (m, 3H), 1.62 (m, 5H), 1.25 (m, 1H), 1.00 (m, 1H), 0.50 (m, 1H), 0.24-0.29 (m, 1H), 0.10 (m, 1H).

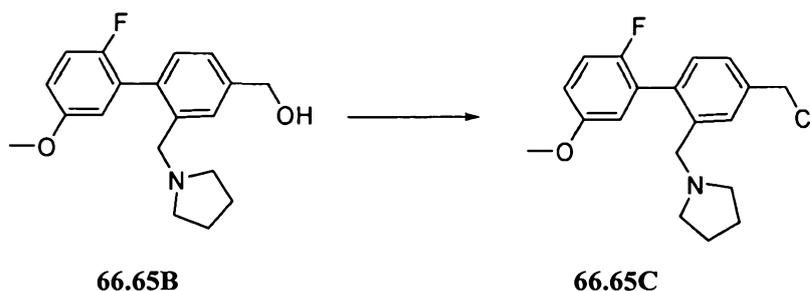
[0878] **Example 66.65**



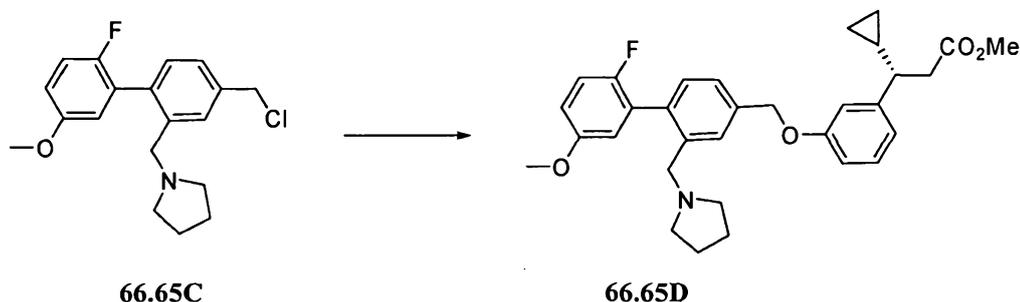
[0879] **Methyl 2'-fluoro-5'-(methoxy)-2-(1-pyrrolidinylmethyl)-1,1'-biphenyl-4-carboxylate (66.65A)**. Compound 66.65A was synthesized using a procedure analogous to that used for 66.64A using pyrrolidine in place of piperidine. MS ESI (pos.) m/e: 344 (M+H)⁺.



[0880] **(2'-Fluoro-5'-(methoxy)-2-(1-pyrrolidinylmethyl)-1,1'-biphenyl-4-yl)methanol (66.65B)**. Compound 66.65B was synthesized using a procedure analogous to that used for 66.64B.



[0881] 1-((4-(Chloromethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)methyl)pyrrolidine (**66.65C**). Compound **66.65C** was synthesized using a procedure analogous to that used for **66.64C**.



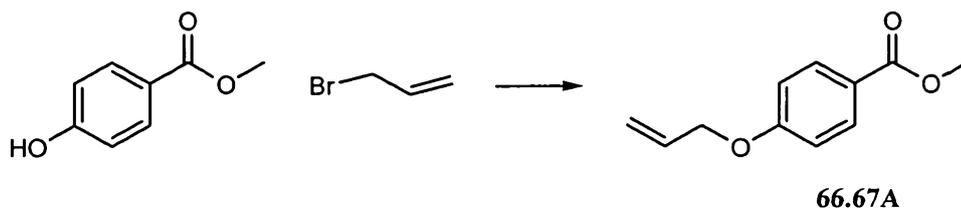
[0882] Methyl (3S)-3-cyclopropyl-3-(3-((2'-fluoro-5'-(methoxy)-2-(1-pyrrolidinylmethyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-((2'-fluoro-5'-(methoxy)-2-(1-pyrrolidinylmethyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (**66.65D**). Compound **66.65D** was synthesized using a procedure analogous to that used for **66.64D**.

[0883] (3S)-3-Cyclopropyl-3-(3-((2'-fluoro-5'-(methoxy)-2-(1-pyrrolidinylmethyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-((2'-fluoro-5'-(methoxy)-2-(1-pyrrolidinylmethyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (**66.65**). Example **66.65** was synthesized using a procedure analogous to that used for **66.64**. After removing solvent, 41 mg of **66.65** (TFA salt) was obtained. MS ESI (neg.) m/e: 502 (M-H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.68(m, 1H), 7.83 (s, 1H), 7.60 (m, 1H), 7.39 (m, 1H), 7.21-7.30 (m, 2H), 7.07 (m, 1H), 6.86-6.96 (m, 4H), 5.17 (s, 2H), 4.04-4.40 (m, 2H), 3.34 (m, 2H), 2.59-2.70 (m, 4H), 2.27 (m, 1H), 1.79 (m, 4H), 1.00 (m, 1H), 0.50 (m, 1H), 0.24 (m, 2H), 0.10 (m, 1H).

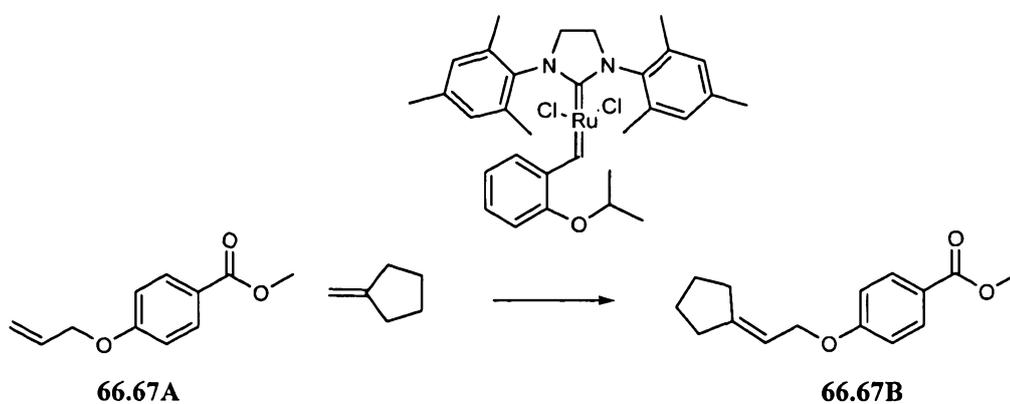
[0884] (3S)-3-(3-(3-(5,5-Dimethylcyclopent-1-enyl)-4-(2-methoxypyridin-4-yl)benzyloxy)phenyl)-3-cyclopropylpropanoic acid or (3R)-3-(3-(3-(5,5-

dimethylcyclopent-1-enyl-4-(2-methoxyppyridin-4-yl)benzyloxy)phenyl)-3-cyclopropylpropanoic acid (66.66). This compound was prepared using the same method described for 66.12 using 2-methoxyppyridin-4-ylboronic acid (commercially available from Asymchem) as the Suzuki coupling reagent. MS ESI (pos.) m/e: 498.2 (M+H)⁺.

[0885] Example 66.67

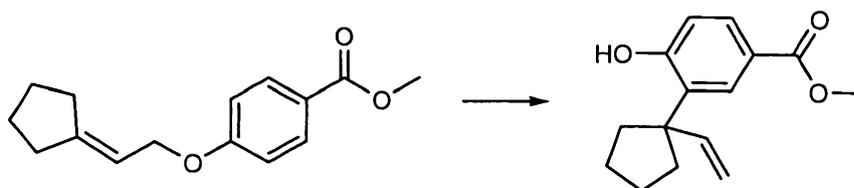


[0886] Methyl 4-(allyloxy)benzoate (66.67A). The reaction mixture of 4-hydroxybenzoic acid, methyl ester (20.0 g, 131.0 mmol), allyl bromide (17.0 g, 138.0 mmol) and potassium carbonate (45.0 g, 329.0 mmol) in DMSO (30.0 mL) was stirred at room temperature for 8 hours. EtOAc (150 mL) was added, and the organic phase was washed with water (30 x 3 mL). The organic layer was dried over MgSO₄. The solvent was removed. The product thus obtained was of sufficient quality for use in the next step without further purification, (25.0 g, yield 99%). ¹H NMR(400 MHz, CDCl₃) δ ppm 7.91 (2 H, m), 6.86 (2 H, m), 5.98 (1 H, dt, J=17.2, 5.3 Hz), 5.35 (1 H, dd, J=17.2, 1.6 Hz), 5.24 (1 H, dd, J=10.6, 1.6 Hz), 4.52 (2 H, d, J=5.5 Hz), 3.81 (3 H, s).

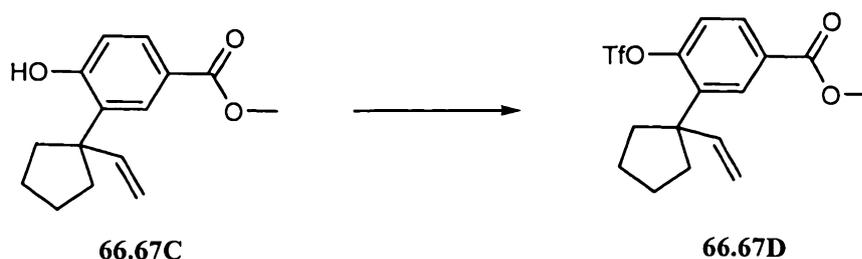


[0887] Methyl 4-(2-cyclopentylideneethoxy)benzoate (66.67B). To a solution of methyl 4-(allyloxy)benzoate 66.67A (3.00 g, 16.0 mmol) and methylenecyclopentane (1.9 g, 23.0 mmol) in DCM (5.0 mL) was added Hoveyda Grubbs reagent (0.39 g, 0.62

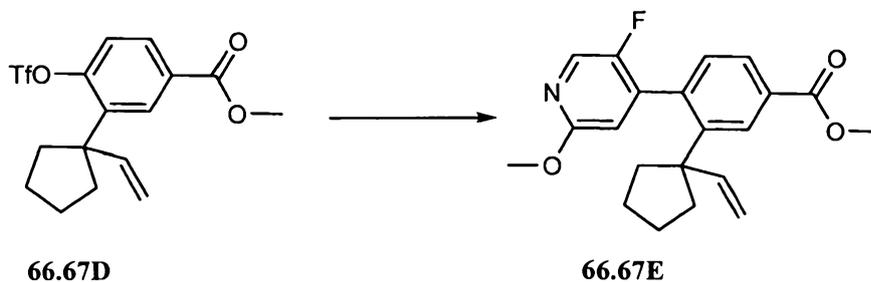
mmol) at room temperature. The resulting reaction mixture was degassed three times and stirred at 55°C under nitrogen overnight. The reaction mixture was purified by Combi Flash silica gel chromatography (hexane/EtOAc 95/5) to give the compound **66.67B**, (2.60 g, yield 68 %). ¹H NMR(500 MHz, CDCl₃) δ ppm 7.82 - 7.93 (2 H, m), 6.80 - 6.88 (2 H, m), 5.44 - 5.56 (1 H, m), 4.47 (2 H, d, J=6.6 Hz), 3.80 (3 H, s), 2.20 - 2.31 (4 H, m), 1.50 - 1.71 (4 H, m).



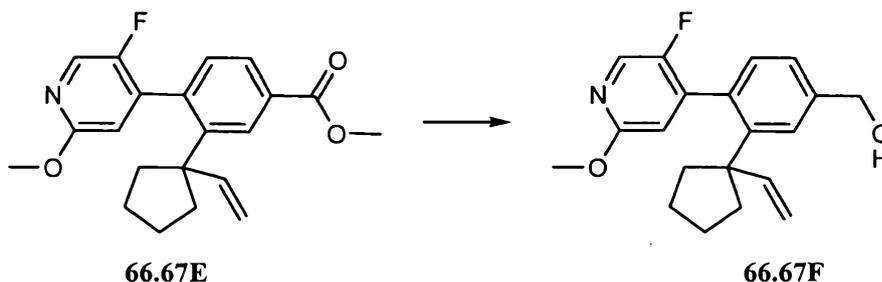
66.67B **66.67C**
[0888] Methyl 4-hydroxy-3-(1-vinylcyclopentyl)benzoate (66.67C). A mixture of methyl 4-(2-cyclopentylideneethoxy) benzoate **66.67B** (0.50g, 2.0 mmol), N,N-diethylaniline (3.2 mL, 20 mmol) and N,O-bis(trimethylsilyl)acetamide (2.5 mL, 10 mmol) in a 20 mL seal tube was heated at 240°C for 48 hours. The reaction was then cooled to room temperature, ether (60 mL) was added, and the mixture was washed with HCl (3N, 20 mL). The organic layer was separated and the solvent was removed. The residue was dissolved in MeOH (10 mL) and HCl (3N, 2 mL) and stirred at room temperature for 30 minutes. Ether (80 mL) was added, and the mixture was washed with NaHCO₃ (30 mL) and brine (15 mL). The organic layer was dried over MgSO₄. After filtering, the solvent was removed. The residue was purified by Combi Flash silica gel column, eluting with hexane/EtOAc (95/5) to give the compound **66.67C**, (0.15g, yield 30 %). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.90 (1 H, d, J=2.2 Hz), 7.80 (1 H, dd, J=8.3, 2.0 Hz), 6.81 (1 H, d, J=8.3 Hz), 5.99 (1 H, dd, J=17.6, 10.5 Hz), 5.77 (1 H, s), 5.18 (1 H, dd, J=10.5, 1.0 Hz), 5.08 (1 H, d, J=17.6 Hz), 3.82 (3 H, s), 1.89 - 2.03 (4 H, m), 1.56 - 1.78 (4 H, m). MS ESI (neg.) m/e: 245.1 (M-H)⁺.



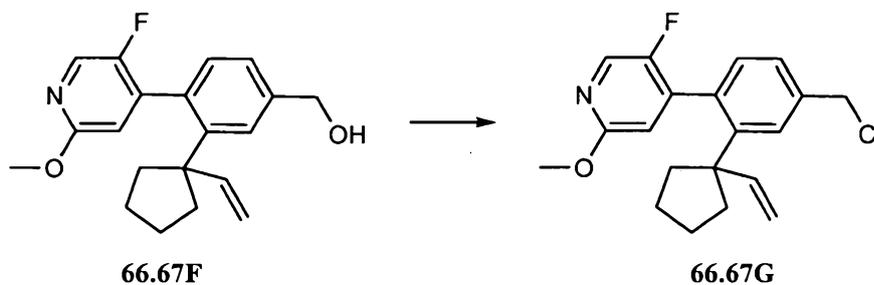
[0889] Methyl 4-(trifluoromethylsulfonyloxy)-3-(1-vinylcyclopentyl)benzoate (66.67D). To a solution of methyl 4-hydroxy-3-(1-vinylcyclopentyl)benzoate **66.67C** (0.19g, 0.77 mmol) and a catalytic amount of DMAP in pyridine (1.5 mL) was slowly added trifluoromethanesulfonic anhydride (0.17 mL, 1.0 mmol) at 0°C. After addition, the reaction mixture was stirred at ambient temperature for 16 hours. EtOAc (70 mL) was added, and the mixture was washed with citric acid (15.0 mL, 1 M in water) and brine (20.0 mL), and then dried with magnesium sulfate. After filtration, the solvent was removed. The desired product **66.67D** was sufficient for use in the next step. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.06 (1 H, d, J=2.3 Hz), 7.87 (1 H, dd, J=8.6, 2.0 Hz), 7.16 (1 H, s), 5.85 (1 H, dd, J=17.2, 10.6 Hz), 4.95 (1 H, d, J=10.6 Hz), 4.72 (1 H, d, J=17.2 Hz), 3.83 (3 H, s), 2.12 - 2.28 (2 H, m), 1.74 - 1.94 (2 H, m), 1.66 (4 H, m).



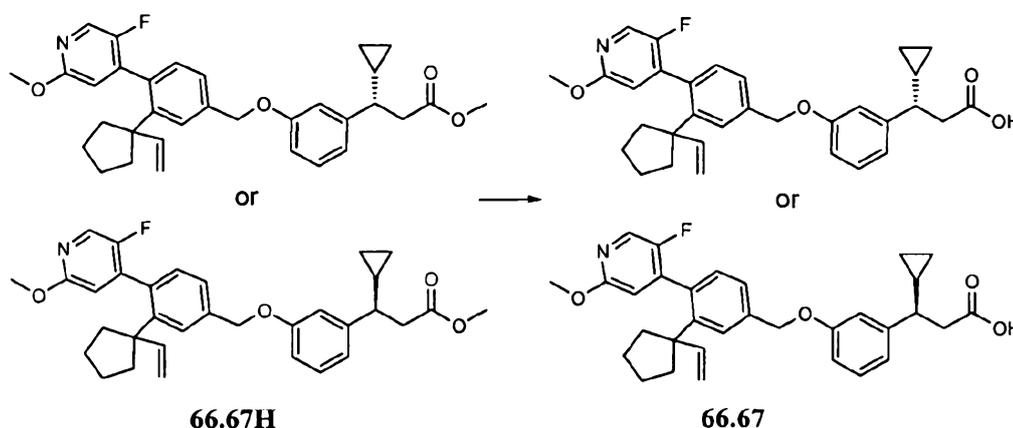
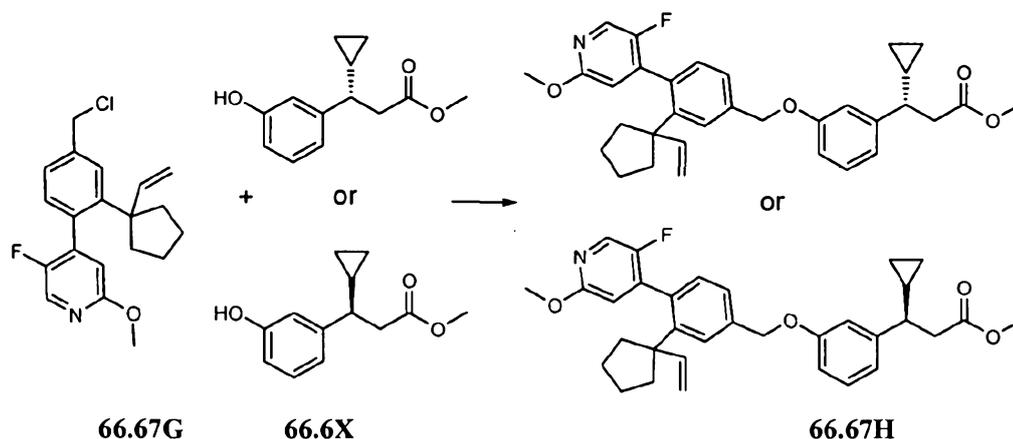
[0890] Methyl 4-(5-fluoro-2-methoxypyridin-4-yl)-3-(1-vinylcyclopentyl)benzoate (66.67E). A mixture of methyl 4-(trifluoromethylsulfonyloxy)-3-(1-vinylcyclopentyl)benzoate **66.67D** (0.29g, 0.8 mmol), 5-fluoro-2-methoxypyridin-4-ylboronic acid (0.2 g, 1.0 mmol) (commercially available from Asymchem), potassium phosphate (0.5 g, 2.0 mmol), S-phos (0.06 g, 0.2 mmol) and palladium acetate (0.02 g, 0.08 mmol) in DMF (1.5 mL) was purged with nitrogen three times. The resulting mixture was heated at 90°C for 2 hours. The reaction mixture was purified by Combi Flash silica gel, eluting with hexane/EtOAc (9/1) to give **66.67E**. ¹H NMR (500 MHz, CDCl₃) δ ppm 8.20 (1 H, d, J=1.7 Hz), 8.00 (1 H, s), 7.91 (1 H, dd, J=7.8, 1.7 Hz), 7.10 (1 H, d, J=8.1 Hz), 6.63 (1 H, d, J=4.9 Hz), 5.87 (1 H, dd, J=17.4, 10.5 Hz), 4.97 (1 H, d, J=10.5 Hz), 4.69 (1 H, d, J=17.4 Hz), 3.98 (3 H, s), 3.85 (3 H, s), 2.00 - 2.20 (1 H, m), 1.80 - 1.96 (1 H, m), 1.51 - 1.75 (6 H, m). MS ESI (pos.) m/e: 355.9 (M+H)⁺.



[0891] **4-(5-Fluoro-2-methoxyphenyl)-3-(1-vinylcyclopentyl)phenyl)methanol (66.67F).** To a solution of methyl 4-(5-fluoro-2-methoxyphenyl)-3-(1-vinylcyclopentyl)benzoate **66.67E** (51.0 mg, 143 μmol) in THF (2.0 mL) was slowly added LAH, (1.0M solution in diethyl ether)(0.30 mL, 287 μmol) at room temperature. The resulting mixture was stirred at 50°C for 1 hour. Standard work up conditions were employed and the solvent was removed. The desired product was used in the next step without further purification. MS ESI (pos.) m/e: 328.2 (M+H)⁺.

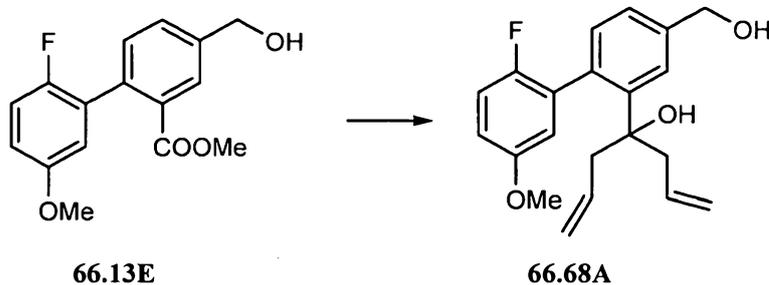


[0892] **4-(4-(Chloromethyl)-2-(1-vinylcyclopentyl)phenyl)-5-fluoro-2-methoxyphenyl (66.67G).** To a solution of (4-(5-fluoro-2-methoxyphenyl)-3-(1-vinylcyclopentyl)phenyl)methanol **66.67F** (47.0 mg, 144 μmol) in DMF (0.01 mL) and DCM (4.0 mL) was slowly added thionyl chloride (14.7 μL , 201 μmol) at 0°C. After addition, the resulting mixture was stirred at room temperature for 1 hour. The solvent was removed, and the desired product was used directly in the next step. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.01 - 8.11 (1 H, m), 7.98 (1 H, m), 7.47 (1 H, s), 6.94 (1 H, d, J=7.8 Hz), 6.69 - 6.82 (1 H, m), 5.80 (1 H, dd, J=17.2, 10.6 Hz), 4.89 (1 H, d, J=10.2 Hz), 4.52 - 4.69 (3 H, m), 3.89 (3 H, s), 1.68 - 1.84 (4 H, m), 1.49 - 1.67 (4 H, m).

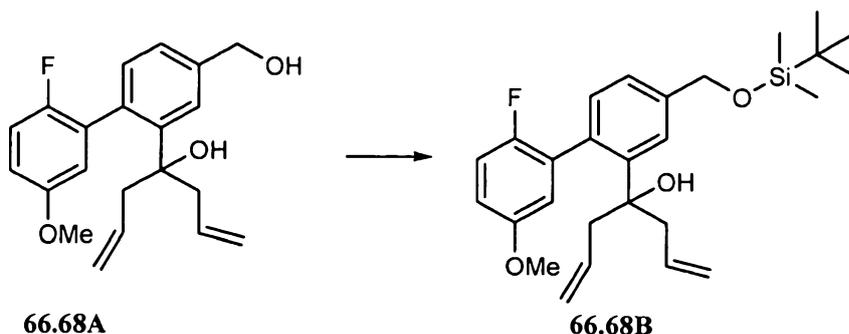


room temperature for 16 hours. LCMS indicated that the reaction was complete. The reaction mixture was brought to a pH of 6 with HCl (3.0 N in water) and purified by preparative HPLC (reversed phase) to give the product **66.67**. $^1\text{H NMR}$ (400 MHz, CD_3CN) δ ppm 7.87 (1 H, s), 7.50 (1 H, d, $J=1.6$ Hz), 7.23 (1 H, dd, $J=7.8, 1.6$ Hz), 7.04 - 7.17 (1 H, m), 6.88 - 6.96 (1 H, m), 6.68 - 6.83 (3 H, m), 6.46 - 6.60 (1 H, m), 5.74 (1 H, dd, $J=17.2, 10.6$ Hz), 5.01 (2 H, s), 4.79 (1 H, d, $J=10.6$ Hz), 4.57 (1 H, d, $J=17.2$ Hz), 3.75 (3 H, s), 2.51 - 2.70 (2 H, m), 2.14 (1 H, td, $J=9.2, 6.3$ Hz), 1.85 - 2.01 (1 H, m), 1.59 - 1.74 (1 H, m), 1.33 - 1.59 (6 H, m), 0.81 - 0.96 (1 H, m), 0.35 - 0.49 (1 H, m), 0.08 - 0.27 (2 H, m, $J=12.2, 12.2, 8.5, 3.9$ Hz), 0.00 (1 H, ddd, $J=9.5, 4.6, 4.3$ Hz). MS ESI (neg.) m/e : 514.3 (M-H) $^+$.

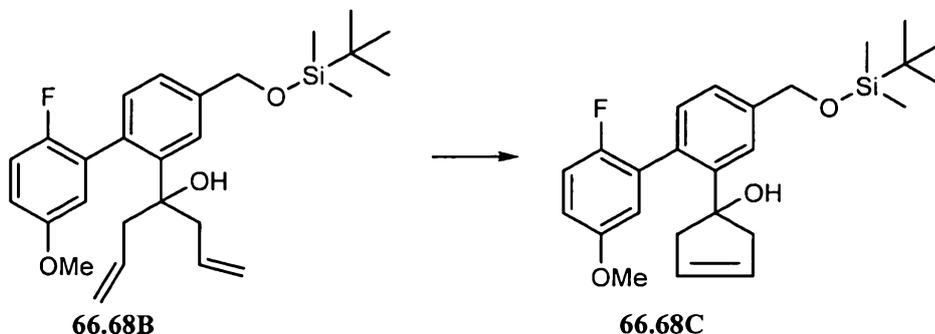
[0895] **Example 66.68**



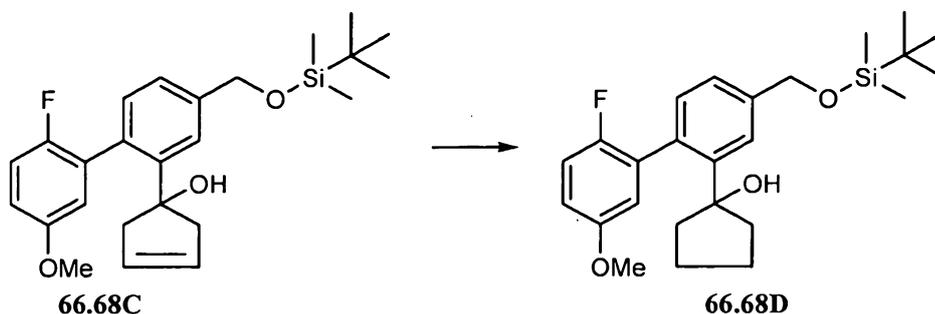
[0896] **4-(2'-Fluoro-4-hydroxymethyl-5'-methoxy-biphenyl-2-yl)-hepta-1,6-dien-4-ol (66.68A)** To a solution of **66.13E** (712 mg, 2453 μmol) in benzene, was added allylmagnesium bromide (24528 μL , 24528 μmol) in ether. The mixture was stirred at room temperature for 1 hour and then quenched with saturated NH_4Cl . EtOAc was added, and the organic layer was washed with water and brine. The organic layer was then dried and concentrated to give a residue which was purified by flash column to give the product as an oil (670mg, 80%).



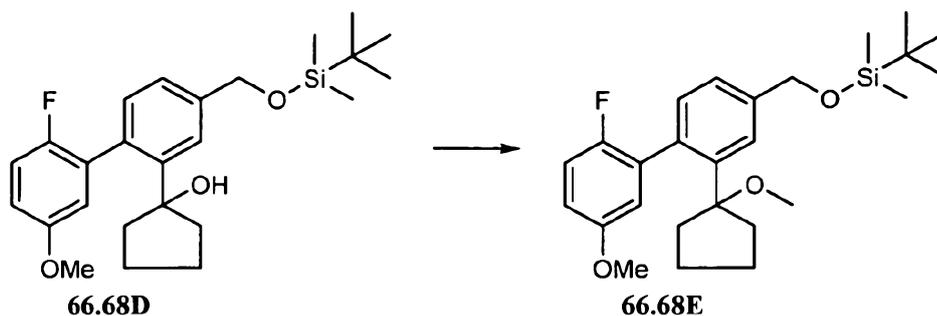
[0897] **4-[4-(tert-Butyl-dimethyl-silyloxymethyl)-2'-fluoro-5'-methoxy-biphenyl-2-yl]-hepta-1,6-dien-4-ol (66.68B)** Compound **66.68B** was synthesized from **66.68A** using a method analogous to the method used to prepare compound **66.13J** from **66.13H**. MS ESI m/e : 457.3 (M+1)⁺.



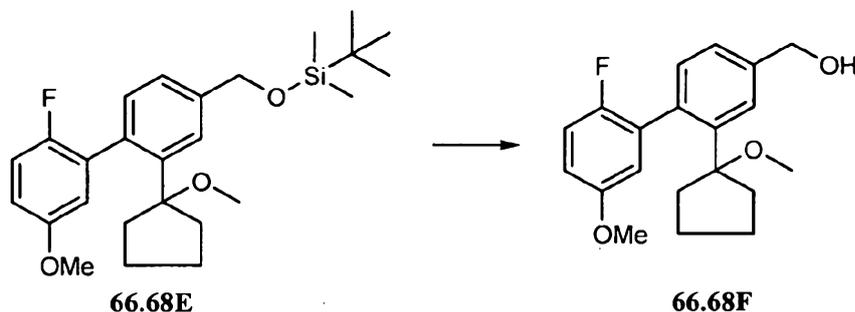
[0898] **1-[4-(tert-Butyl-dimethyl-silyloxymethyl)-2'-fluoro-5'-methoxy-biphenyl-2-yl]-cyclopent-3-enol (66.68C)**. To a solution of **66.68B** (259mg, 567 μmol) in 20 mL of DCM, was added (under a nitrogen atmosphere) Grubbs reagent in 20 mL of DCM by syringe. The resulting mixture was stirred at room temperature for 2 hours. Solvent was then removed in vacuo to give a residue which was purified by Combiflash chromatography to give the product as an oil (110mg, 45%). MS ESI m/e : 429.3 (M+H)⁺.



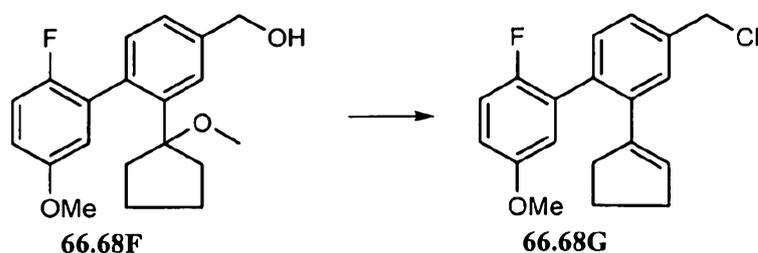
[0899] **1-[4-(tert-Butyl-dimethyl-silyloxymethyl)-2'-fluoro-5'-methoxy-biphenyl-2-yl]-cyclopentanol (66.68D)** To a solution of **66.68C** (100 mg, 212 μmol) in EtOAc, was added 10% PtO₂/C (50mg). The mixture was then stirred under a hydrogen atmosphere for 0.5 hours, the solid was filtered away, and the filtrate was concentrated to give the product as an oil which was used in the next step.



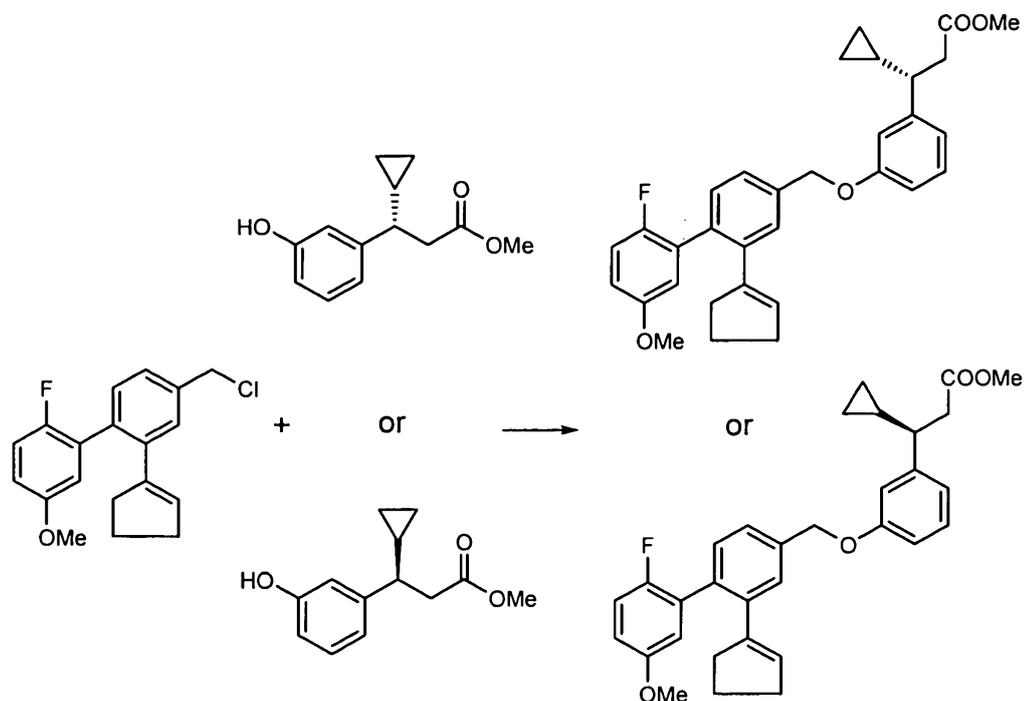
[0900] tert-Butyl-[2'-fluoro-5'-methoxy-2-(1-methoxy-cyclopentyl)-biphenyl-4-ylmethoxy]-dimethyl-silane (66.68E) Compound **66.68E** was synthesized from **66.68D** using a method analogous to the method used to prepare compound **66.41E** from **66.41D**. MS ESI m/e : 445.3 (M+H)⁺.



[0901] [2'-Fluoro-5'-methoxy-2-(1-methoxy-cyclopentyl)-biphenyl-4-yl]-methanol (66.68F). To a solution of **66.68E** (66 mg, 168 μ mol) in MeOH, was added PPTS (11 mg, 45 μ mol), and the mixture was stirred for 16 hours. Solvent was then removed in vacuo to give a residue which was purified by Combiflash chromatography to give the product as an oil (30mg, 61%). MS ESI m/e : 331.2 (M+H)⁺.



[0902] 4-Chloromethyl-2-cyclopent-1-enyl-2'-fluoro-5'-methoxy-biphenyl (66.68G). Compound **66.68G** was synthesized from **66.68F** using a method analogous to the method used to prepare compound **66.12D** from **66.12C**. MS ESI m/e : 317.1 (M+1)⁺.

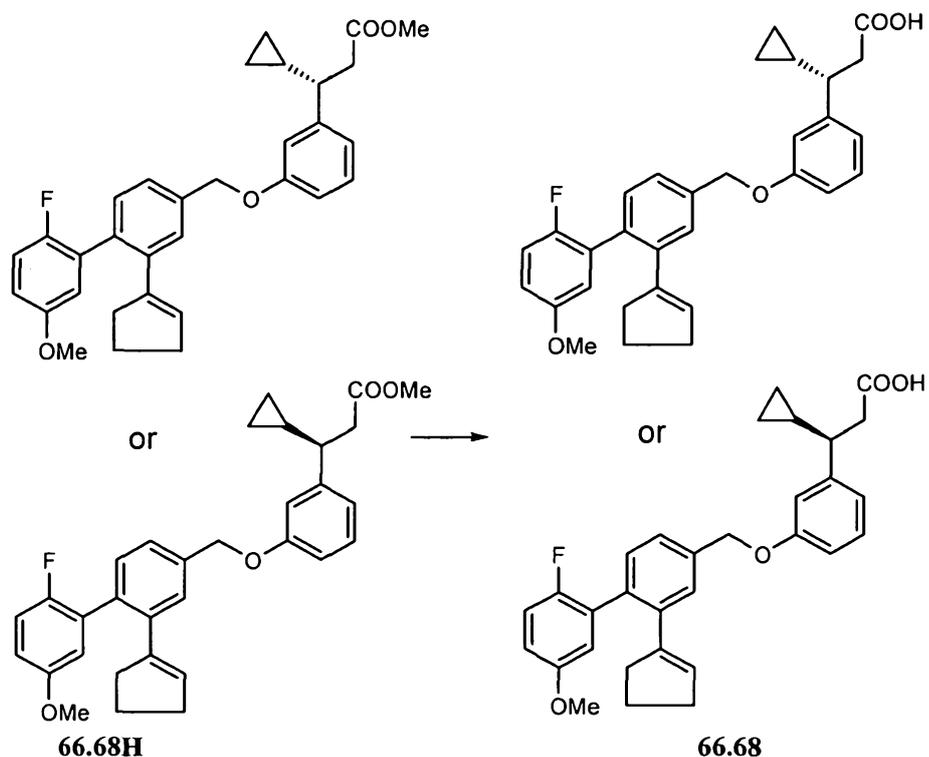


66.68G
[0903]

66.6X
(S)-3-[3-(2-Cyclopent-1-enyl-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy)-phenyl]-3-cyclopropyl-propionic acid methyl ester or (R)-3-[3-(2-cyclopent-1-enyl-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy)-phenyl]-3-

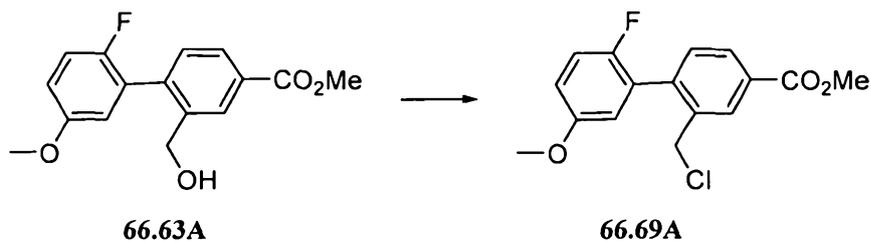
66.68H

cyclopropyl-propionic acid methyl ester (66.68H). Compound 66.68H was synthesized from 66.68G and 66.6X using a method analogous to the method used to prepare compound 66.13P. MS ESI m/e : 501.3 (M+H)⁺.

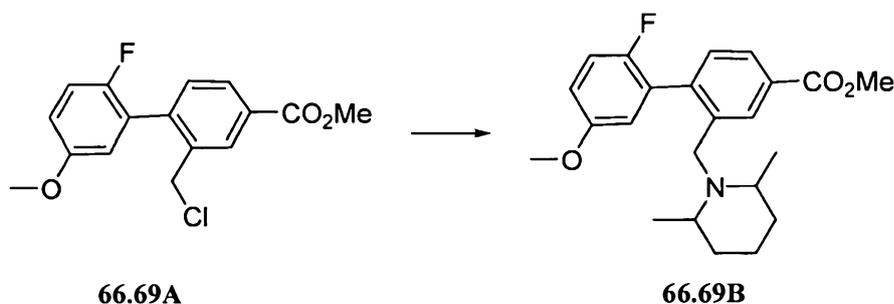


[0904] **(S)-3-[3-(2-Cyclopent-1-enyl-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy)-phenyl]-3-cyclopropyl-propionic acid or (R)-3-[3-(2-cyclopent-1-enyl-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy)-phenyl]-3-cyclopropyl-propionic acid (66.68).** Compound **66.68** was synthesized from **66.68H** by a method analogous to that used to prepare compound **66.13** from **66.13P**. MS ESI m/e : 487.2 ($M+1$)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.44 (m, 1H), 7.37 (m, 1H), 7.29 (m, 1H), 7.24 (m, 1H), 6.99 (m, 1H), 6.79-6.89 (m, 5H), 5.52 (m, 1H), 5.07 (s, 2H), 3.78 (s, 3H), 2.78 (m, 2H), 2.36 (m, 4H), 1.85 (m, 2H), 1.27 (m, 1H), 1.03 (m, 1H), 0.58 (m, 1H), 0.43 (m, 1H), 0.28 (m, 1H), 0.17 (m, 1H).

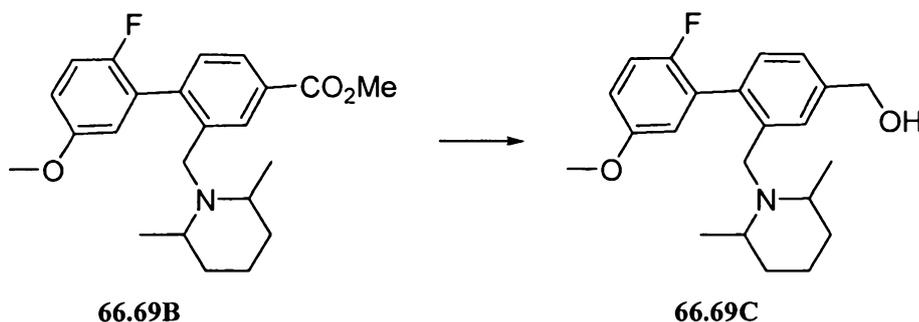
[0905] **Example 66.69**



[0906] **Methyl 2-(chloromethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.69A)**. Thionyl chloride (available from Aldrich) (4.46 g, 37.5 mmol) was added to a solution of **66.63A** in DCM (6 mL). The reaction mixture was stirred at room temperature for 2 hours and then at 50°C for 3 hours. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:9 EtOAc / hexane) and gave **66.69A** (386 mg) as a colorless oil.

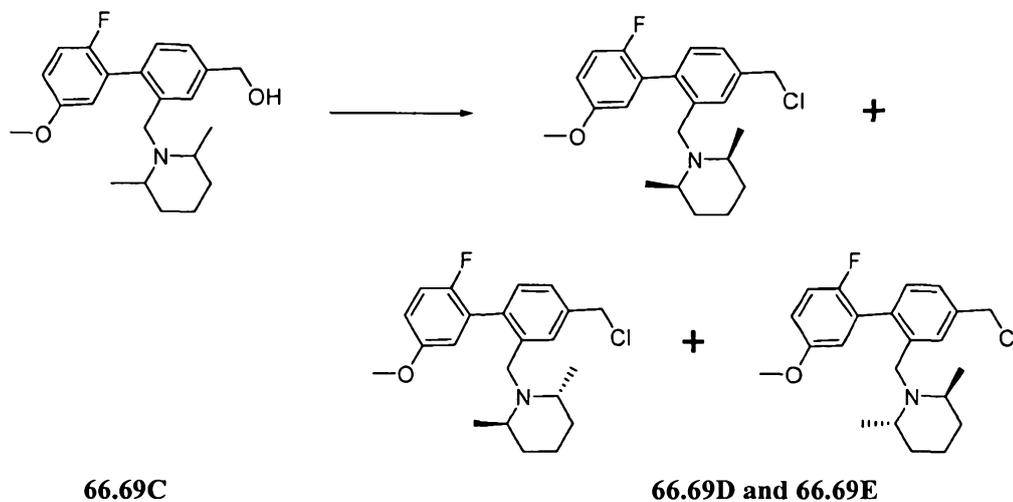


[0907] **Methyl 2-((2,6-dimethyl-1-piperidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.69B)**. A mixture of **66.69A** (0.094 g, 0.30 mmol), 2,6-dimethylpiperidine (0.069 g, 0.61 mmol) (commercially available from Aldrich) and cesium carbonate (0.20 g, 0.61 mmol) in DMSO (4 mL) was stirred at 70°C for 24 hours. The product was purified by reverse phase HPLC to give **66.69B** in 30% yield.

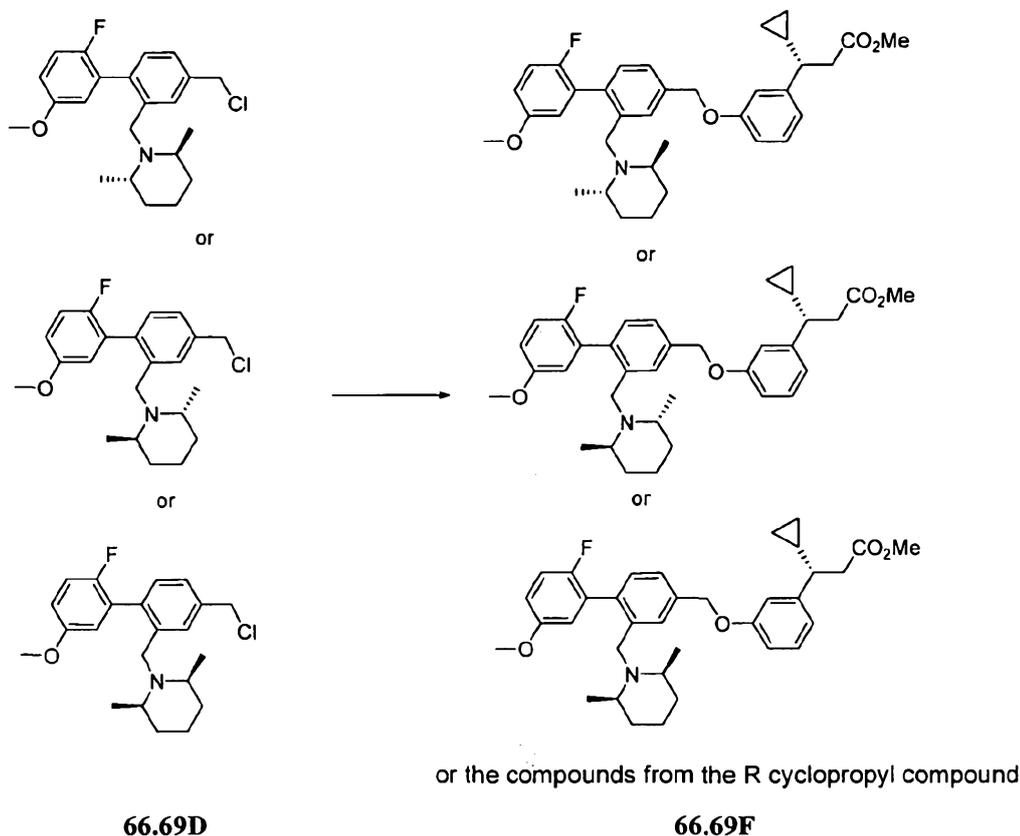


[0908] **(2-((2,6-Dimethyl-1-piperidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (66.69C)**. LAH (1.0 M solution in THF) (0.088 mL, 0.088 mmol) was added slowly to a solution of **66.69B** (0.034 g, 0.088 mmol) in THF (1 mL). The resulting mixture was stirred at room temperature for 25 minutes and then was poured into brine (2 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate. After removing solvent, the residue

was purified by flash chromatography (silica gel, 1:1 EtOAc / hexane) and gave **66.69C** (22 mg) as a colorless oil.



[0909] **(2R,6S)-1-((4-(Chloromethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)methyl)-2,6-dimethylpiperidine** and **(2S,6S)-1-((4-(chloromethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)methyl)-2,6-dimethylpiperidine** and **(2R,6R)-1-((4-(chloromethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)methyl)-2,6-dimethylpiperidine (66.69D)**. Thionyl chloride (available from Aldrich) (0.11 mL, 1.5 mmol) was added to a solution of **66.69C** (0.022 g, 0.062 mmol) in DCM(0.2 mL) and it was stirred at room temperature for 4 hours. The product was purified by reverse phase HPLC to give **66.69D** (6mg) and **66.69E** (8mg). One of these included the racemic mixture of the trans R,R and S,S compounds and the other was the R,S cis compound. The configuration of cis- and trans- 2,6-dimethylpiperidine was not confirmed.



[0910] Methyl (3S)-3-cyclopropyl-3-(3-(((2-(((2R,6S)-2,6-dimethyl-1-piperidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3S)-3-cyclopropyl-3-(3-(((2-(((2R,6R)-2,6-dimethyl-1-piperidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate and methyl (3S)-3-cyclopropyl-3-(3-(((2-(((2S,6S)-2,6-dimethyl-1-piperidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate; or methyl (3R)-3-cyclopropyl-3-(3-(((2-(((2R,6S)-2,6-dimethyl-1-piperidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2-(((2R,6R)-2,6-dimethyl-1-piperidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate and methyl (3R)-3-cyclopropyl-3-(3-(((2-(((2S,6S)-2,6-dimethyl-1-piperidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.69F). The title ester compound was synthesized from 66.69D using the same procedure used to prepare 66.62F.

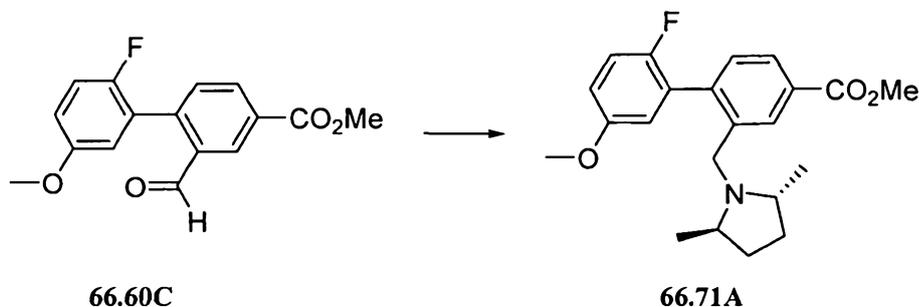
1H), 4.11-4.16 (m, 1H), 3.97 (m, 1H), 3.66 (m, 1H), 2.66-2.83 (m, 3H), 2.33 (m, 1H), 1.69 (m, 2H), 1.55 (m, 2H), 1.25-1.34 (m, 6H), 1.01-1.13 (m, 2H), 0.77-0.86 (m, 1H), 0.60 (m, 1H), 0.45 (m, 1H), 0.29 (m, 1H), 0.18 (m, 1H).

[0912] Methyl (3S)-3-cyclopropyl-3-(3-(((2-(((2R,6S)-2,6-dimethyl-1-piperidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3S)-3-cyclopropyl-3-(3-(((2-(((2R,6R)-2,6-dimethyl-1-piperidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate and methyl (3S)-3-cyclopropyl-3-(3-(((2-(((2S,6S)-2,6-dimethyl-1-piperidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate; or methyl (3R)-3-cyclopropyl-3-(3-(((2-(((2R,6S)-2,6-dimethyl-1-piperidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2-(((2R,6R)-2,6-dimethyl-1-piperidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate and methyl (3R)-3-cyclopropyl-3-(3-(((2-(((2S,6S)-2,6-dimethyl-1-piperidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (66.70A). The methyl ester 66.70A was obtained from 66.69E using the same procedure described above with respect to 66.69.

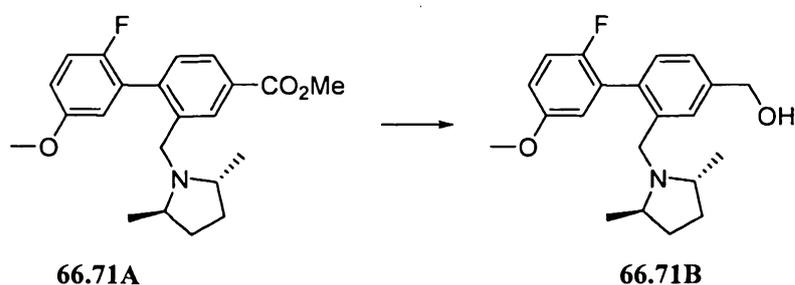
[0913] (3S)-3-Cyclopropyl-3-(3-(((2-(((2R,6S)-2,6-dimethyl-1-piperidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-(((2R,6R)-2,6-dimethyl-1-piperidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid and (3S)-3-cyclopropyl-3-(3-(((2-(((2S,6S)-2,6-dimethyl-1-piperidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid; or (3R)-3-cyclopropyl-3-(3-(((2-(((2R,6S)-2,6-dimethyl-1-piperidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-(((2R,6R)-2,6-dimethyl-1-piperidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid and (3R)-3-cyclopropyl-3-(3-(((2-(((2S,6S)-2,6-dimethyl-1-piperidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.70). Example 66.70 was prepared from 66.70A using a procedure similar to that used to prepare 66.65. After removing solvent, 3.6 mg of 66.70 (TFA salt) was obtained. MS ESI (neg.) m/e: 544 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 9.50(m, 1H), 7.73-7.77 (m, 1H), 7.57-7.59 (m, 1H), 7.36-7.39 (m, 1H), 7.13-7.24 (m, 2H), 6.88-6.90 (m, 3H), 6.78-6.88 (m, 2H), 5.22 (s, 2H), 4.30-4.60

(m, 1H), 4.13-4.14 (m, 1H), 3.97 (m, 1H), 3.67 (m, 1H), 2.66-2.85 (m, 3H), 2.33 (m, 1H), 1.72 (m, 2H), 1.55 (m, 2H), 1.25-1.33 (m, 6H), 1.01-1.13 (m, 2H), 0.77-0.86 (m, 1H), 0.60 (m, 1H), 0.45 (m, 1H), 0.29 (m, 1H), 0.18 (m, 1H).

[0914] **Example 66.71**

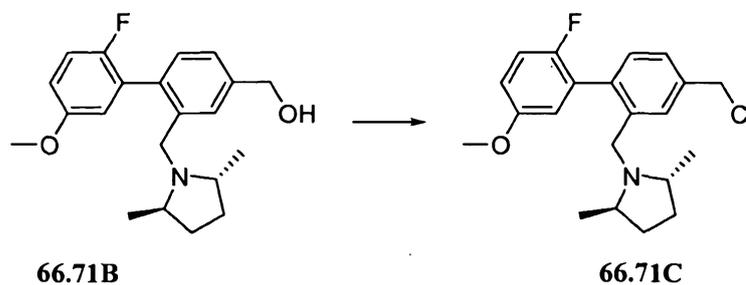


[0915] **Methyl 2-(((2R,5R)-2,5-dimethyl-1-pyrrolidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (66.71A)**. Sodium cyanoborohydride (0.071 g, 1.1 mmol) was added to a solution of **66.60C** (0.180 g, 0.62 mmol) and (2R,5R)-2,5-dimethylpyrrolidine (available from Aldrich) (0.073 g, 0.74 mmol) in MeOH (3 mL). The reaction was stirred at 110°C for 30 minutes and then was diluted with EtOAc (100 mL). The mixture was washed with an aqueous Na₂CO₃ solution and brine, and dried over anhydrous sodium sulfate. After filtration, solvent was removed, and the residue was purified by flash chromatography (silica gel, 1:6 EtOAc / hexane) and gave **66.71A** (32 mg).

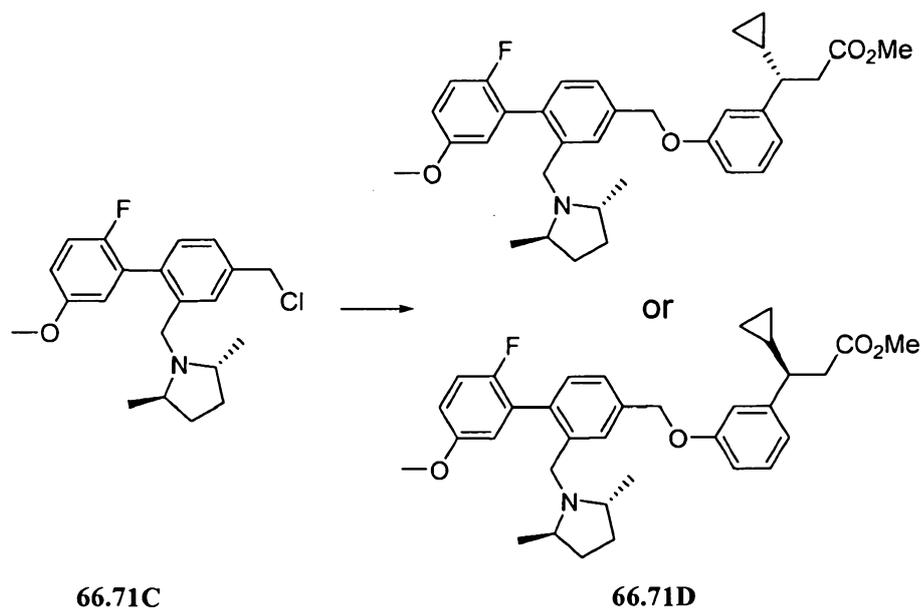


[0916] **(2-(((2R,5R)-2,5-Dimethyl-1-pyrrolidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (66.71B)**. LAH (1.0 M solution in THF) (0.086 mL, 0.086 mmol) was added slowly to a solution of **66.71A** (0.032 g, 0.086 mmol) in THF (1.5 mL) and the mixture was stirred at room temperature for 33 minutes. The mixture was poured into brine (2 mL) and extracted with EtOAc (3 x 30 mL). The

combined organic phase was dried over anhydrous sodium sulfate and filtered. After removing solvent, **66.71B** (29 mg) was obtained.

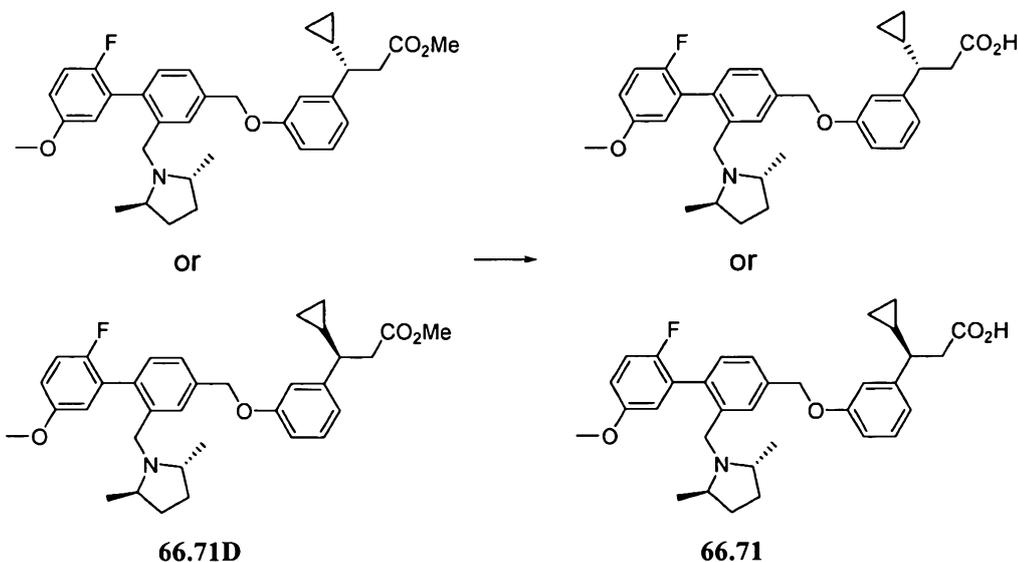


[0917] **(2R,5R)-1-((4-(Chloromethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)methyl)-2,5-dimethylpyrrolidine (66.71C)**. Thionyl chloride (0.25 g, 2.1 mmol) was added to a solution of **66.71B** (0.029 g, 0.084 mmol) in DCM (0.7 mL) and the mixture was stirred at room temperature for 1 hour. After removing solvent, **66.71C** (28 mg) was obtained.



[0918] **Methyl (3S)-3-cyclopropyl-3-(3-(((2R,5R)-2,5-dimethyl-1-pyrrolidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methoxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2R,5R)-2,5-dimethyl-1-pyrrolidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-**

yl)methyl)oxy)phenyl)propanoate (66.71D). The title compound was prepared from 66.71C and 66.6X using a procedure similar to that described for 66.62F.

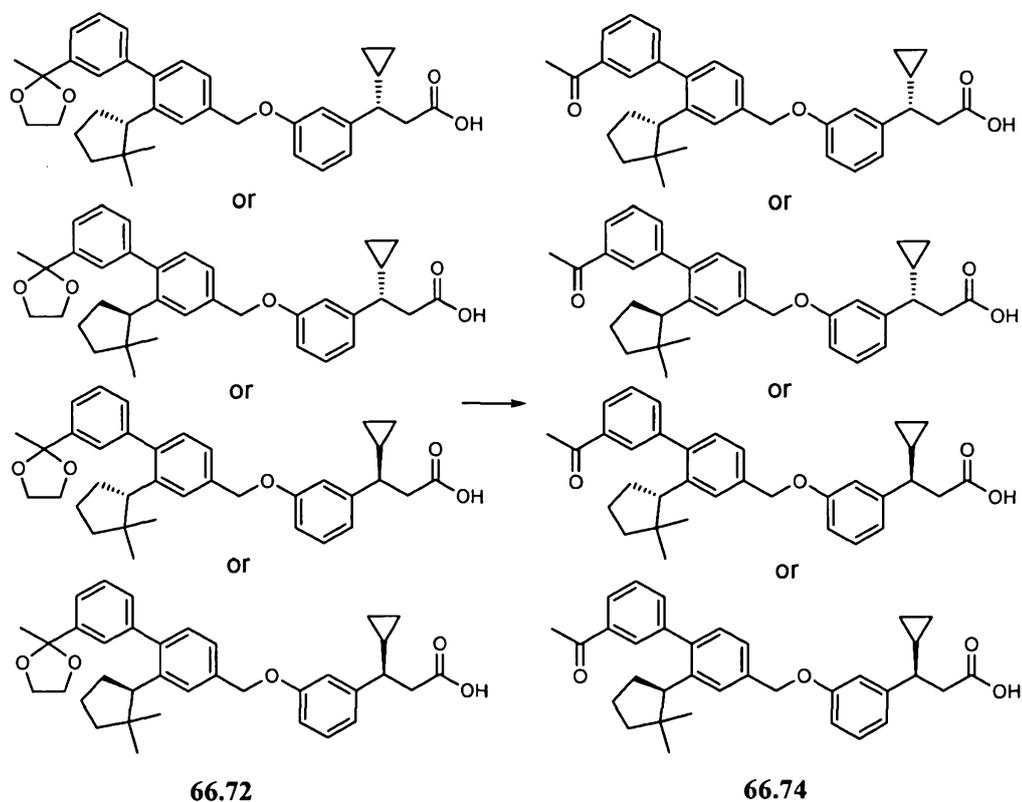


[0919] (3S)-3-Cyclopropyl-3-(3-(((2-(((2R,5R)-2,5-dimethyl-1-pyrrolidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-(((2R,5R)-2,5-dimethyl-1-pyrrolidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.71). Example 66.71 was prepared from 66.71D using a procedure analogous to that used to prepare 66.65. After removing solvent, 15 mg of 66.71 (TFA salt) was obtained. MS ESI (neg.) m/e: 530 (M-H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.55(m, 1H), 7.87 (m, 1H), 7.62-7.64 (m, 1H), 7.41-7.43 (m, 1H), 7.31 (m, 1H), 7.22 (m, 1H), 7.08 (m, 1H), 6.93 (m, 2H), 6.87 (m, 2H), 5.19 (s, 2H), 4.10-4.40 (m, 1H), 3.78 (s, 3H), 3.60-3.80(m, 1H), 2.65 (m, 1H), 2.27 (m, 1H), 2.08 (m, 1H), 1.56 (m, 2H), 1.26 (m, 1H), 1.14 (m, 1H), 0.85-1.05 (m, 3H), 0.85 (m, 1H), 0.49 (m, 1H), 0.20-0.30 (m, 2H), 0.11 (m, 1H).

[0920] (S)-3-(3-((S)-3-((S)-2,2-Dimethylcyclopentyl)-4-(3-(2-methyl-1,3-dioxolan-2-yl)phenyl)benzyloxy)phenyl)-3-cyclopropylpropanoic acid or stereoisomer thereof (66.72). This compound was prepared as the same method described for 66.6 using 66.6X and 3-(2-methyl-1,3-dioxolan-2-yl)phenylboronic acid as the Suzuki coupling reagent to form the biphenyl reagent. MS ESI (neg.) m/e: 553.3 (M-H)⁺.

[0921] (3S)-3-(3-(((2-(1-Azepanylmethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclopropylpropanoic acid or (3R)-3-(3-(((2-(1-azepanylmethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclopropylpropanoic acid (66.73). The title compound was synthesized using a procedure analogous to that described in 66.64 starting using azepane (commercially available from Aldrich) in place of piperidine. After removing solvent, 66.73 (26 mg) was obtained as the TFA salt. MS ESI (neg.) m/e: 530 (M-H)⁻. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.37 (m, 1H), 7.91 (m, 1H), 7.63-7.65 (m, 1H), 7.41-7.43 (m, 1H), 7.22-7.33 (m, 1H), 7.06-7.10 (m, 1H), 6.88-6.98 (m, 4H), 5.18 (s, 2H), 4.05-4.20 (m, 1H), 3.79 (s, 3H), 2.90-3.17 (m, 4H), 2.67 (m, 2H), 2.30 (m, 1H), 1.49 (m, 8H), 1.00 (m, 1H), 0.52 (m, 1H), 0.26 (m, 2H), 0.11 (m, 1H).

[0922] **Example 66.74**



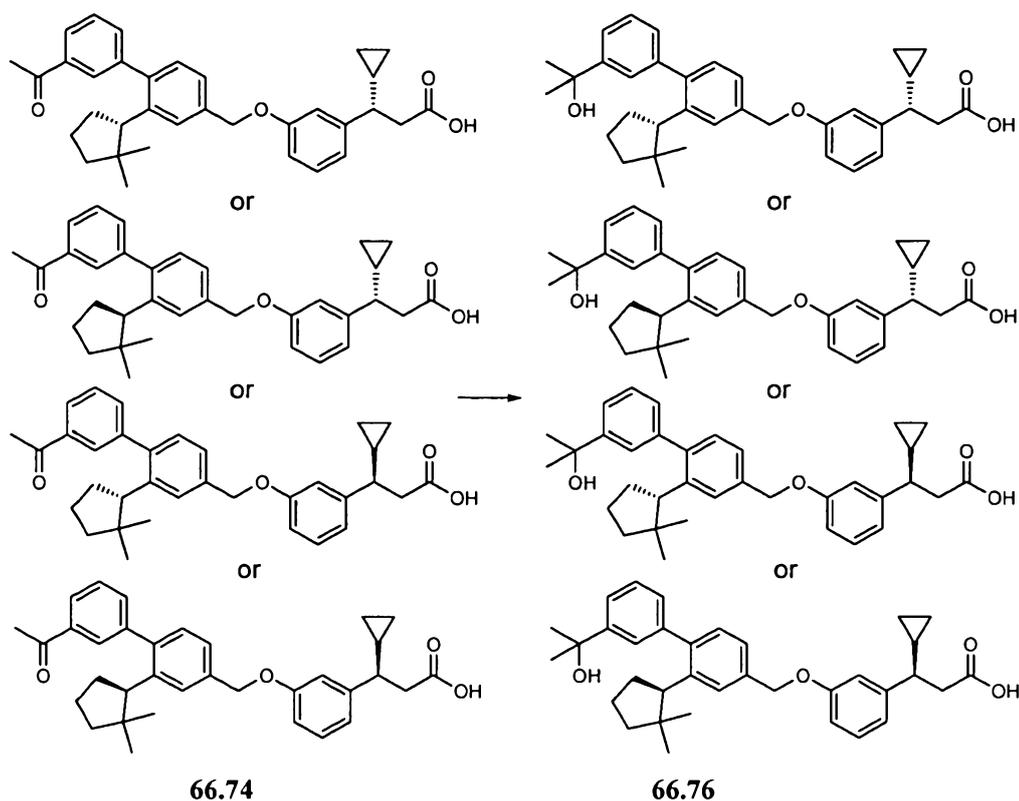
[0923] (S)-3-(3-(((S)-3-((S)-2,2-Dimethylcyclopentyl)-4-(3-acetylphenyl)benzyloxy)phenyl)-3-cyclopropylpropanoic acid or stereoisomer thereof (66.74). To a flask with 66.72 (39 mg, 70 μmol) was added PPTS (5.3 mg, 21 μmol), 2 mL acetone, 0.1 mL water. The reaction was heated to reflux. After about 3

hours, the reaction had a little starting material left and was stored in refrigerator for 48 hours. A little more PPTS was added, and the reaction was heated for two more hours. The reaction was then concentrated, diluted with EtOAc and washed with NaHCO₃ and brine. Silica gel chromatography afforded 28 mg of **66.74** (78%). MS ESI (neg.) m/e: 509.0 (M-H)⁺.

[0924] **(3S)-3-Cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-(((2S)-2-methyl-1-piperidinyl)methyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-(((2S)-2-methyl-1-piperidinyl)methyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (66.75).**

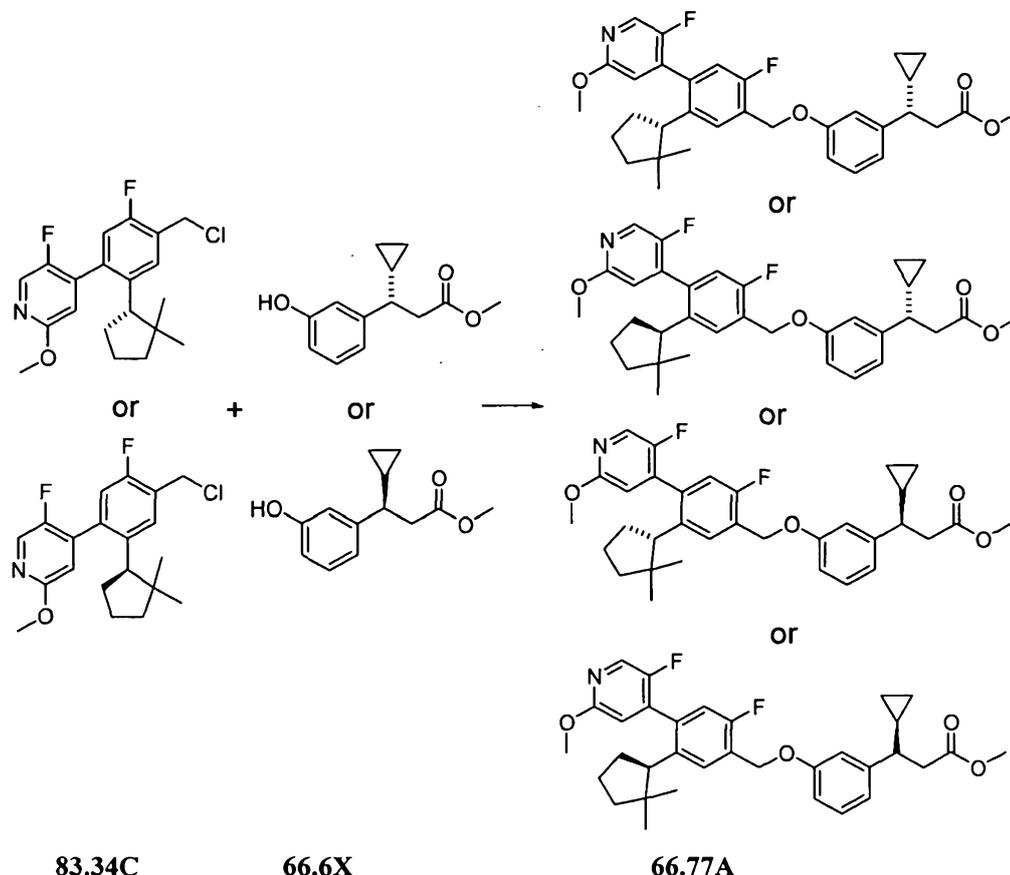
The title compound was synthesized using a procedure analogous to that described in **66.64** starting using (S)-2-methylpiperidine (commercially available from Aldrich) in place of piperidine. After removing solvent, **66.75** (5 mg) was obtained as the TFA salt. MS ESI (neg.) m/e: 530 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 10.60 (m, 1H), 7.74 (m, 1H), 7.57 (d, 1H), 7.34 (m, 1H), 7.10-7.17 (m, 2H), 6.85-7.00 (m, 3H), 6.60-6.80 (m, 2H), 5.23 (m, 2H), 4.70 (m, 1H), 4.10-3.20 (m, 1H), 3.81 (m, 3H), 3.05 (m, 1H), 2.60-2.90 (m, 3H), 2.35 (m, 1H), 1.90-2.06 (m, 1H), 1.65-1.80 (m, 1H), 1.40-1.55 (m, 1H), 1.27 (m, 3H), 0.90-1.20 (m, 2H), 0.60 (m, 1H), 0.47 (m, 1H), 0.30 (m, 1H), 0.19 (m, 1H).

[0925] **Example 66.76**



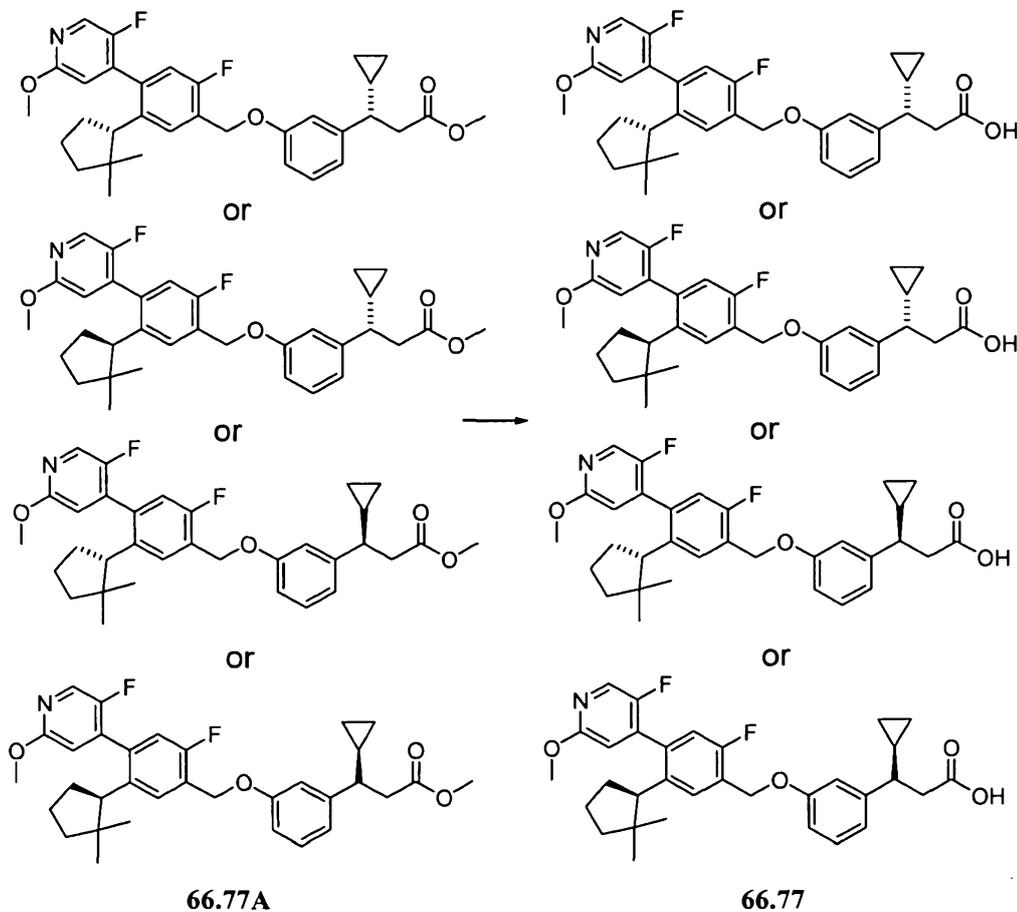
[0926] (S)-3-(3-((S)-3-((S)-2,2-dimethylcyclopentyl)-4-(3-(2-hydroxypropan-2-yl)phenyl)benzyloxy)phenyl)-3-cyclopropylpropanoic acid or stereoisomer thereof (**66.76**). Example **66.74** (26.5 mg, 52 μ mol) was azeotroped with toluene. Anhydrous THF was added, and the reaction was cooled in an ice-bath. Methylmagnesium bromide (3.0 M in diethyl ether)(52 μ L, 156 μ mol) was added, and the reaction was stirred at room temperature for 1.5 hours and then quenched with NH_4Cl . Purification with silica gel chromatography afforded 14 mg of product **66.76** (51%). MS ESI (neg.) m/e: 525.1 (M-H)⁺.

[0927]

Example 66.77

[0928] **Methyl (3S)-3-cyclopropyl-3-(3-(((5-((1S)-2,2-dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)phenyl)propanoate or methyl (3S)-3-cyclopropyl-3-(3-(((5-((1R)-2,2-dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((5-((1S)-2,2-dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((5-((1R)-2,2-dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)phenyl)propanoate (66.77A).** To a vial containing **66.6X** (0.0251 g, 0.114 mmol) in 1.50 mL dry DMF was added cesium carbonate (0.0447 g, 0.137 mmol). The mixture was stirred at room temperature for 10 minutes, and then **83.34C** (0.0447 g, 0.122 mmol) was added. After 22 hours, the reaction was diluted with water and then the mixture was extracted five times with EtOAc. The combined organic layers were then washed one time with brine and dried over anhydrous magnesium sulfate. The solid was filtered off, and the solvent was

concentrated. The residue was purified by silica gel flash chromatography (0-30% EtOAc/hexane) to afford **66.77 A** (53.6 mg, 86 % yield). MS ESI (pos.) m/e: 550.3 (M+H)⁺.



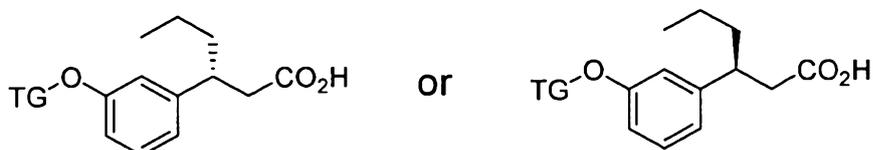
[0929] (3S)-3-Cyclopropyl-3-(3-(((5-((1S)-2,2-dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((5-((1R)-2,2-dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((5-((1S)-2,2-dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((5-((1R)-2,2-dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)phenyl)propanoic acid (**66.90**). A pre-mixed solution of 2 M NaOH (0.5 mL, 1.00 mmol), MeOH (1 mL), and THF (1 mL) was added to a vial containing **66.77A** (0.0536 g, 0.0975 mmol). The resulting mixture was stirred at room temperature and monitored with TLC and LC-MS. After 24 hours, the

mixture was diluted with water and acidified with 1M aqueous HCl solution and then extracted five times with EtOAc. The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel flash chromatography (0-30% EtOAc/hexane) to afford **66.77** (41.2 mg, 79 % yield). MS ESI (pos.) m/e: 536.2 (M+H)⁺. MS ESI (neg.) m/e: 534.1 (M-H)⁻.

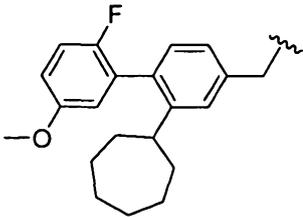
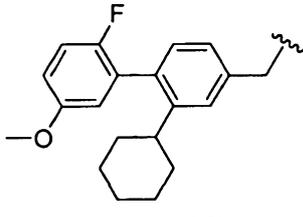
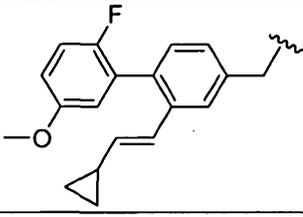
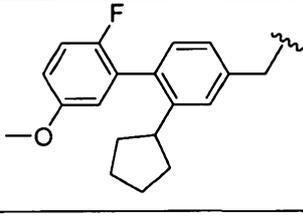
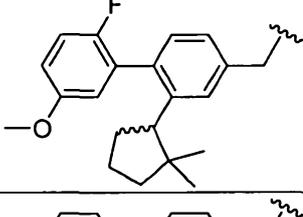
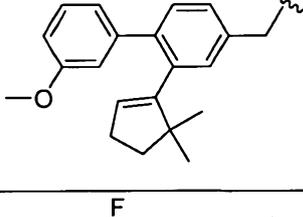
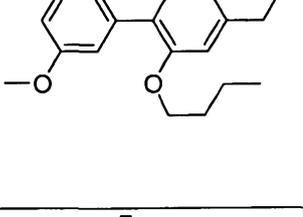
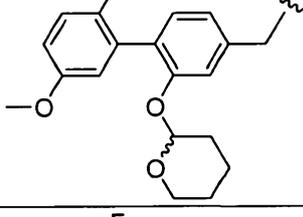
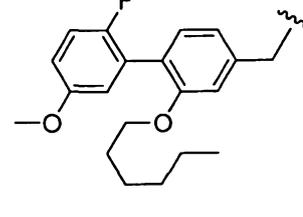
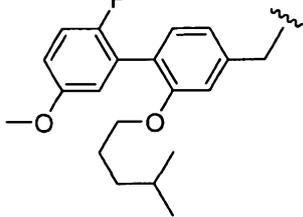
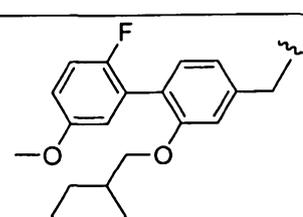
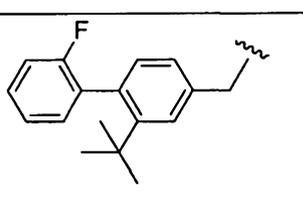
[0930] **Example 67**

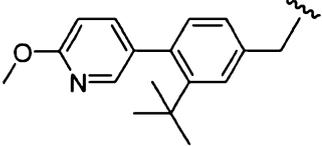
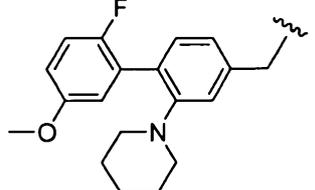
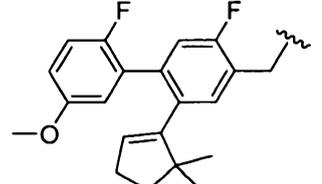
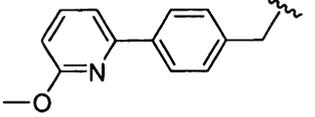
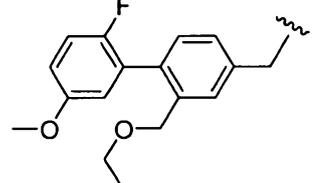
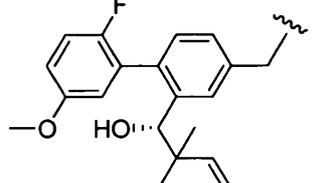
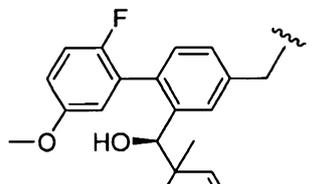
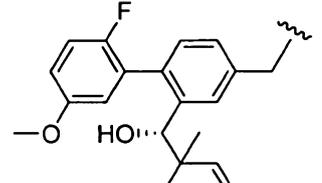
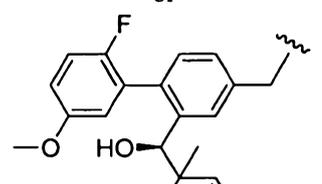
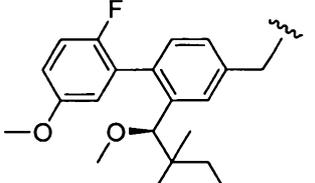
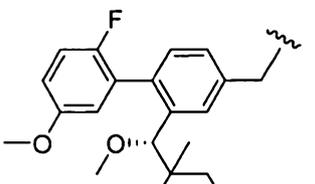
[0931] The following compounds were prepared from **43.6** and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Each of the compounds in the following table were prepared using the same enantiomer of the phenol.

Table 7



Compound	TG	Compound	TG
67.1		67.2	
67.3		67.4	
67.5		67.6	

Compound	TG	Compound	TG
67.7		67.8	
67.9		67.10	
67.11		67.12	
67.13		67.14	
67.15		67.16	
67.17		67.18	

Compound	TG	Compound	TG
67.19		67.20	
67.21		67.22	
67.23		67.24	 <p style="text-align: center;">or</p> 
67.25	 <p style="text-align: center;">or</p>  <p>but not the same one as 67.24</p>	67.26	 <p style="text-align: center;">or</p> 

Compound	TG	Compound	TG
67.27		67.28	

[0932] (3R)-3-(3-(((2'-Fluoro-5'-(methoxy)-2-(pentyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2'-fluoro-5'-(methoxy)-2-(pentyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.1). MS ESI (neg.) m/e: 507.2 (M-H).

[0933] (3R)-3-(3-(((2-(Cycloheptyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-(cycloheptyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.2). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.30 (1 H, d, J=7.6 Hz), 7.23 (1 H, t, J=7.8 Hz), 7.00 - 7.06 (3 H, m), 6.81 - 6.90 (5 H, m), 5.07 (2 H, s), 4.42 (1 H, dt, J=7.8, 3.8 Hz), 3.80 (3 H, s), 3.05 - 3.11 (1 H, m), 2.63 (2 H, dd, J=7.3, 5.6 Hz), 1.87 - 1.93 (2 H, m), 1.67 - 1.75 (2 H, m), 1.56 - 1.65 (4 H, m), 1.49 - 1.53 (4 H, m), 1.34 - 1.41 (2 H, m), 1.15 - 1.24 (2 H, m), 0.84 - 0.88 (3 H, t, J=7.3 Hz).

[0934] (3R)-3-(3-(((2-(1,1-Dimethylethyl)-2',3-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-2',3-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.3). MS ESI (neg.) m/e: 991.5 (2M-H)⁺, 495.2 (M-H)⁺.

[0935] (3R)-3-(3-(((2-((1E)-3,3-Dimethyl-1-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-((1E)-3,3-dimethyl-1-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.4). MS ESI (neg.) m/e: 503.2 (M-H)⁺.

[0936] (3R)-3-(3-(((2-(4,4-Dimethyl-1-cyclohexen-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-(4,4-dimethyl-1-cyclohexen-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.5). MS ESI (neg.) m/e: 529.3 (M-H)⁺.

[0937] (3R)-3-(3-(((2-(1-Cyclohepten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-(1-cyclohepten-1-

yl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.6). MS ESI (neg.) m/e: 515.2 (M-H)⁺.

[0938] (3R)-3-(3-(((2-Cycloheptyl-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-cycloheptyl-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.7). MS ESI (neg.) m/e: 517.3 (M-H)⁺.

[0939] (3R)-3-(3-(((2-Cyclohexyl-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-cyclohexyl-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.8). MS ESI (neg.) m/e: 503.2 (M-H)⁺.

[0940] (3R)-3-(3-(((2-((E)-2-Cyclopropylethenyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-((E)-2-cyclopropylethenyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.9). MS ESI (neg.) m/e: 975.4 (2M-H)⁺, 487.2 (M-H)⁺.

[0941] (3R)-3-(3-(((2-Cyclopentyl-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-cyclopentyl-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.10). MS ESI (neg.) m/e: 979.5 (2M-H)⁺, 489.2 (M-H)⁺.

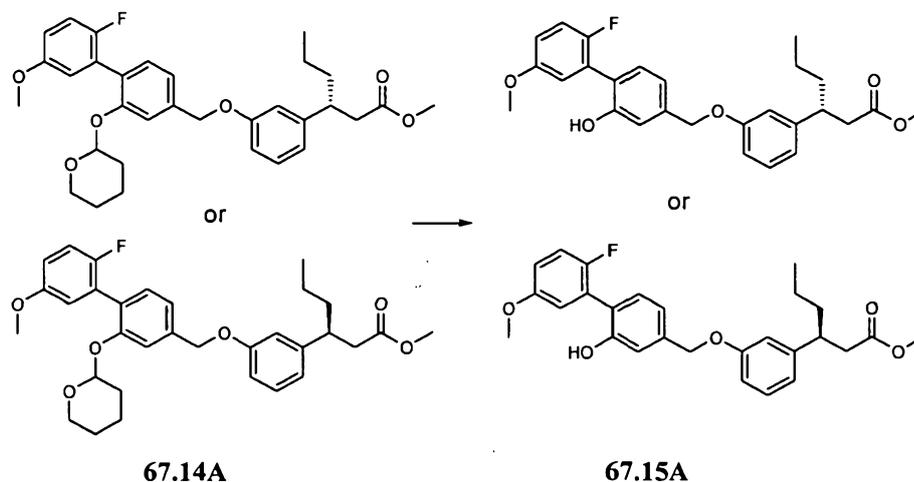
[0942] (3R)-3-(3-(((2-(2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-(2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.11). MS ESI (neg.) m/e: 497.4 (M-H).

[0943] (3R)-3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-3'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-3'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.12). MS ESI (neg.) m/e: 497.4 (M-H).

[0944] (3R)-3-(3-(((2-(Butyloxy)-3'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-(butyloxy)-3'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.13). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.35 (d, 1H), 7.31 (t, 1H), 7.23 (t, 1H), 7.13 (m, 2H), 7.07 (m, 2H), 6.87 (m, 3H), 6.81 (bd, 1H), 5.06 (s, 2H), 3.99 (t, 2H), 3.84 (s, 3H), 3.08 (m, 1H), 2.63 (m, 2H), 1.71 (m, 2H), 1.60 (m, 2H), 1.43 (m, 2H), 1.18 (m, 2H), 0.92 (t, 3H), 0.85 (t, 3H).

[0947] (3R)-3-(3-(((2'-Fluoro-5'-(methoxy)-2-(tetrahydro-2H-pyran-2-yloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2'-fluoro-5'-(methoxy)-2-(tetrahydro-2H-pyran-2-yloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.14). To a solution of 67.14A (15.0 mg, 28 μ mol) in THF/MeOH (2/1) (1.5 mL) was added LiOH (0.500 mL, 500 μ mol). The resulting mixture was stirred overnight at 23°C, quenched with excess 1N HCl, and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by chromatography (0 to 40% EtOAc/hexanes) to afford a 67.14 (9.6 mg, 66% yield): MS ESI (neg.) m/e: 521.2 (M-H).

[0948] **Example 67.15**



[0949] Methyl (3R)-3-(3-(((2'-fluoro-2-hydroxy-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoate or methyl (3S)-3-(3-(((2'-fluoro-2-hydroxy-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoate (67.15A). To a solution of 67.14A (295 mg, 550 μ mol) in MeOH (2.5 mL) was added PPTS (13.8 mg, 55.0 μ mol) at room temperature. The mixture was heated overnight, cooled to room temperature, diluted with EtOAc, washed with water and brine, dried (MgSO₄), and concentrated. The crude product was purified by silica gel flash chromatography (0-25% EtOAc/hexane) to afford 67.15A (132.5 mg, 53.3% yield) as a colorless oil.

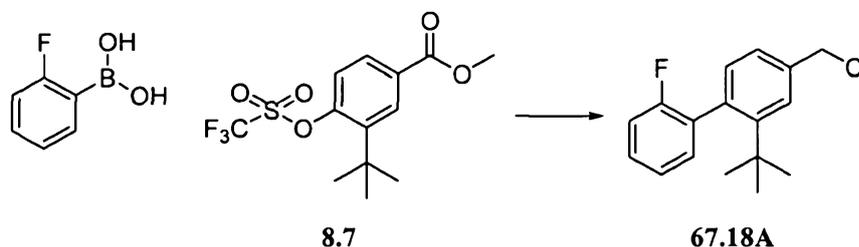
[0950] (3R)-3-(3-(((2'-Fluoro-2-(hexyloxy)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2'-fluoro-2-(hexyloxy)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.15). Example 67.15 was synthesized from 67.15A by a method analogous to that used to prepare

compound **27** using 1-bromohexane which is available from Aldrich. MS ESI (neg.) m/e: 521.2 (M-H).

[0951] **(3R)-3-(3-(((2'-Fluoro-5'-(methoxy)-2-((4-methylpentyl)oxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2'-fluoro-5'-(methoxy)-2-((4-methylpentyl)oxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.16).** Example **67.16** was synthesized from **67.15A** by a method analogous to that used to prepare compound **27** using 1-bromo-4-methylpentane which is commercially available from Aldrich. ¹H NMR (500 MHz, CDCl₃) δ ppm 7.30 (1 H, d, J=8.1 Hz), 7.24 (1 H, t, J=7.8 Hz), 6.97 - 7.10 (3 H, m), 6.79 - 6.92 (5 H, m), 5.07 (2 H, s), 3.97 (2 H, t, J=6.5 Hz), 3.80 (3 H, s), 3.05 - 3.12 (1 H, m), 2.58 - 2.69 (2 H, m), 1.47 - 1.71 (5 H, m), 1.12 - 1.33 (4 H, m), 0.76 - 0.91 (9 H, m).

[0952] **(3R)-3-(3-(((2-((Cyclohexylmethyl)oxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-((cyclohexylmethyl)oxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.17).** Example **67.17** was synthesized from **67.15A** by a method analogous to that used to prepare compound **27** using cyclohexylmethyl bromide which is commercially available from Alfa Aesar. ¹H NMR (500 MHz, CDCl₃) δ ppm 7.31 (1 H, d, J=7.2 Hz), 7.21 - 7.28 (1 H, m), 7.01 - 7.10 (3 H, m), 6.81 - 6.92 (5 H, m), 5.08 (2 H, s), 3.82 (3 H, s), 3.79 (2 H, d, J=5.9 Hz), 3.06 - 3.14 (1 H, m), 2.65 (2 H, dd, J=7.4, 3.3 Hz), 1.55 - 1.78 (8 H, m), 1.08 - 1.32 (5 H, m), 0.93 - 1.05 (2 H, m), 0.84 - 0.90 (3 H, m).

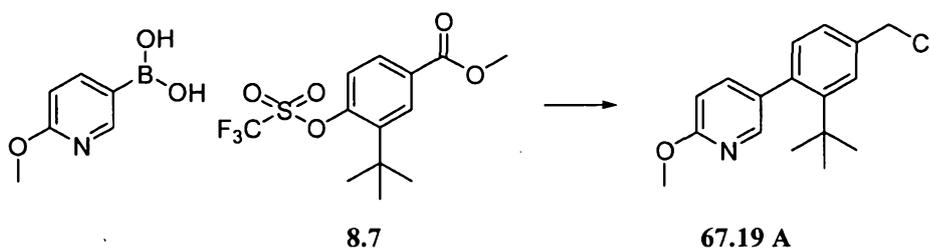
[0953] **Example 67.18**



[0954] **4-(Chloromethyl)-2-(1,1-dimethylethyl)-2'-fluoro-1,1'-biphenyl (67.18A).** The formation of chloromethyl compound **67.18A** was conducted in an analogous manner to Example **8.7-8.10**, described herein using 2-fluorobenzeneboronic acid (commercially available from Aldrich) to yield **67.18A** as a colorless oil (532.3 mg, 80 % yield). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.63 (1 H, d, J=1.6 Hz), 7.48 (1 H, m), 7.35 (4 H, m), 6.97 (1 H, d, J=7.8 Hz), 4.83 (2 H, s), 1.16 (9 H, s).

[0955] (3R)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.18). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 67.18A and 43.6 (derived from peak one from the chiral separation of 43.4 from the OD-column), described herein) to yield 67.18 (41.8 mg, 82 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.64 (1 H, d, *J*=1.6 Hz), 7.37 (2 H, m), 7.29 (2 H, m), 7.18 (2 H, m), 7.09 (1 H, m), 6.92 (3 H, m), 5.10 (2 H, s), 3.15 (1 H, m), 2.65 (2 H, ddd, *J*=17.6, 15.7, 7.4 Hz), 1.69 (2 H, m), 1.29 (12 H, m), 0.88 (3 H, t, *J*=7.4 Hz). MS ESI (neg.) *m/e*: 447.1 (M-H)⁺.

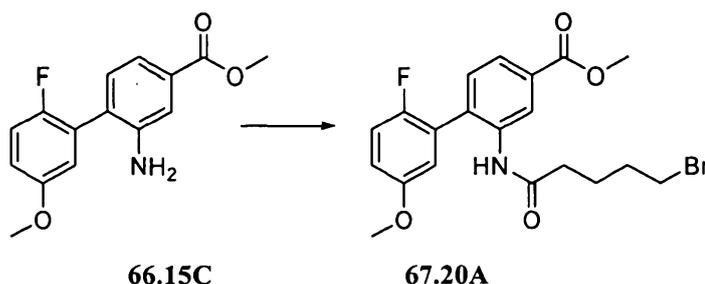
[0956] **Example 67.19**



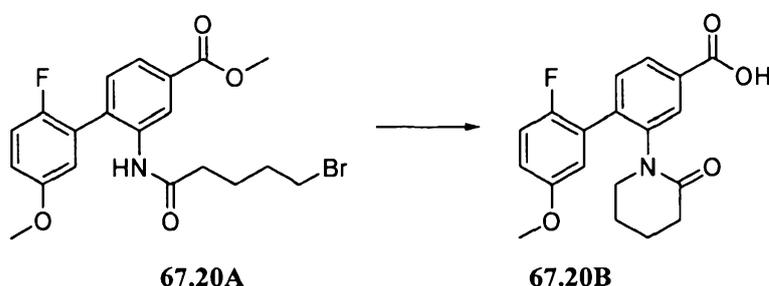
[0957] 5-(4-(Chloromethyl)-2-(1,1-dimethylethyl)phenyl)-2-(methoxy)pyridine (67.19A). The formation of the chloride was conducted in an analogous manner to Example 8.7-8.10, described herein using 6-(methoxy)-3-pyridinylboronic acid which is commercially available from Aldrich to yield 67.19A MS ESI (pos.) *m/e*: 290.2 (M+H)⁺.

[0958] (3R)-3-(3-(((3-(1,1-Dimethylethyl)-4-(6-(methoxy)-3-pyridinyl)phenyl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((3-(1,1-dimethylethyl)-4-(6-(methoxy)-3-pyridinyl)phenyl)methyl)oxy)phenyl)hexanoic acid (67.19). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 67.19A and 43.6 (derived from peak one from the chiral separation of 43.4 from the OD-column), described herein) to yield 67.19. ¹H NMR (400 MHz, CDCl₃) δ ppm 8.08 (1 H, d, *J*=2.3 Hz), 7.61 (1 H, d, *J*=1.6 Hz), 7.50 (1 H, dd, *J*=8.4, 2.5 Hz), 7.32 (2 H, m), 7.04 (1 H, d, *J*=7.8 Hz), 6.90 (3 H, m), 6.78 (1 H, d, *J*=8.6 Hz), 5.09 (2 H, s), 4.01 (3 H, s), 3.15 (1 H, m), 2.65 (2 H, ddd, *J*=17.6, 15.7, 7.4 Hz), 1.69 (2 H, m), 1.28 (11 H, m), 0.87 (3 H, t, *J*=7.4 Hz). MS ESI (neg.) *m/e*: 460.1 (M-H)⁺.

[0959] **Example 67.20**

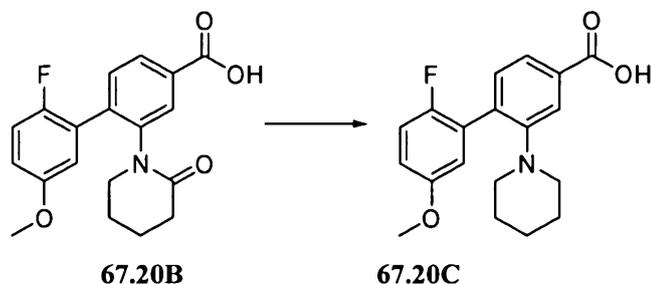


[0960] **Methyl 2-((5-bromopentanoyl)amino)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (67.20 C).** To a dry round bottom flask containing **66.15C** (0.7779 g, 2.83 mmol) was added dry chloroform (8 mL) at 0°C. After five minutes, 5-bromovaleryl chloride (0.5 mL, 3.73 mmol)(commercially available from Aldrich) was added followed by dropwise addition of dry pyridine (0.31 mL, 3.80 mmol). The reaction mixture was allowed to warm to room temperature and monitored with TLC and LC-MS. After 3 hours, the reaction was diluted with DCM and washed twice with saturated aqueous sodium bicarbonate solution, twice with water, and once with brine. The organic layer was dried over anhydrous sodium sulfate then filtered and concentrated. The residue was purified by recrystallization from isopropanol to afford **67.20A** as an off white solid (726.2 mg, 59% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.78 (1 H, s), 7.91 (1 H, d, J=7.8 Hz), 7.36 (1 H, d, J=7.8 Hz), 7.15 (1 H, t, J=9.2 Hz), 7.08 (1 H, s), 6.97 (1 H, dt, J=9.0, 3.7 Hz), 6.81 (1 H, dd, J=5.9, 3.1 Hz), 3.94 (3 H, s), 3.83 (3 H, s), 3.39 (2 H, t, J=6.3 Hz), 2.28 (2 H, t, J=7.0 Hz), 1.89 (2 H, m), 1.82 (2 H, m).

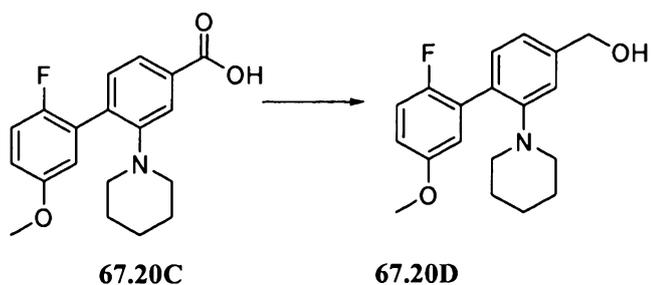


[0961] **2'-Fluoro-5'-(methoxy)-2-(2-oxo-1-piperidinyl)-1,1'-biphenyl-4-carboxylic acid (67.20B).** To a dry vial containing **67.20A** (0.5858 g, 1.337 mmol) was added dry DMF (25 mL). The mixture was stirred at 0 °C for about 15 minutes, then potassium tert-butoxide (0.3766 g, 3.356 mmol) was carefully added in portions. The mixture was heated to 145°C and monitored with TLC and LC-MS. After 2.5 hours, the reaction was cooled to room temperature and then carefully quenched with 2 M aqueous

citric acid solution. After extracting three times with DCM, the organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified with silica gel flash chromatography (0-25% MeOH in DCM) to afford **67.20B** as an oil (440.1 mg, 96% yield). MS ESI (neg.) m/e: 342.0 (M-H)⁻.

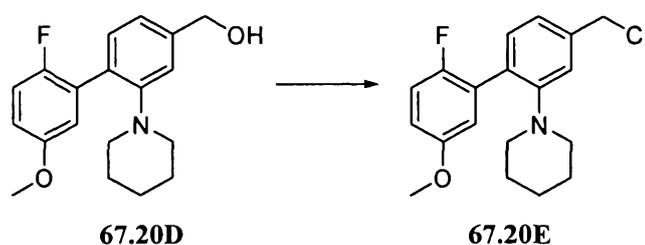


[0962] **2'-Fluoro-5'-(methoxy)-2-(1-piperidinyl)-1,1'-biphenyl-4-carboxylic acid (67.20C)**. To a cooled solution of **67.20B** (0.4401 g, 1.282 mmol) in dry THF (8 mL) at 0 °C was added borane-THF complex, 1.0 M in THF (2.5 mL, 2.5 mmol) dropwise. Upon complete addition, the reaction was maintained at 0 °C and monitored by TLC and LCMS. After 3 hours, water was added to quench the reaction, and the resulting solution was extracted three times with EtOAc. The organic extractions were combined and washed successively with saturated aqueous sodium bicarbonate, water, and then brine. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified with silica gel flash chromatography (0-25% MeOH in DCM) to afford **67.20C** as an oil (292.9 mg, 69% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.85 (2 H, m), 7.36 (1 H, d, J=7.8 Hz), 7.11 (2 H, m), 6.86 (1 H, dt, J=8.9, 3.6 Hz), 3.83 (3 H, s), 2.85 (4 H, m), 1.46 (6 H, m).



[0963] **(2'-Fluoro-5'-(methoxy)-2-(1-piperidinyl)-1,1'-biphenyl-4-yl)methanol (67.20D)**. To a cooled solution of **67.20C** (0.2929 g, 0.8893 mmol) in dry THF (10 mL) at 0 °C was added LAH (1M in THF)(1.8 mL, 1.8 mmol). Upon complete

addition, the reaction was maintained at 0°C and was monitored by TLC and LCMS. After 2 hours, 1N NaOH was added to quench the reaction (gas evolution occurred). The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified by flash chromatography (SiO₂ gel 60, eluted with 0%-50% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to afford **67.20D** as a colorless oil (231.8 mg, 83% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.25 (1 H, d, J=9.0 Hz), 7.11 (4 H, m), 6.82 (1 H, dt, J=9.0, 3.5 Hz), 4.71 (2 H, d, J=5.5 Hz), 3.81 (3 H, s), 2.81 (4 H, m), 1.69 (1 H, s), 1.43 (6 H, m).



[0964] **1-(4-(Chloromethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)piperidine (67.20E)**. To a solution of **67.20D** (0.2318 g, 0.73 mmol) in dry DMF (0.03 mL) and dry DCM (3 mL) was added thionyl chloride (0.13 mL, 1.8 mmol) at 0 °C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was diluted with DCM and then washed once with saturated aqueous sodium bicarbonate and once with brine. After drying over anhydrous magnesium sulfate, filtering, and removing the solvent under reduced pressure, the residue was purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **67.20E** (86.3 mg, 35% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.16 (1 H, m), 7.00 (4 H, m), 6.72 (1 H, dt, J=9.0, 3.5 Hz), 4.50 (2 H, s), 3.71 (3 H, s), 2.71 (4 H, m), 1.34 (6 H, m).

[0965] **(3R)-3-(3-(((2'-Fluoro-5'-(methoxy)-2-(1-piperidinyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2'-fluoro-5'-(methoxy)-2-(1-piperidinyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.20)**. The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using **67.20E** and **43.6** (derived from peak one from the chiral separation of **43.4** from the OD-column), described herein) to yield **67.19** (37.2 mg, 72% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.19 (2 H, m), 7.07 (4 H, m), 6.80 (4 H, m), 4.95 (2 H, s), 3.72 (3 H, s),

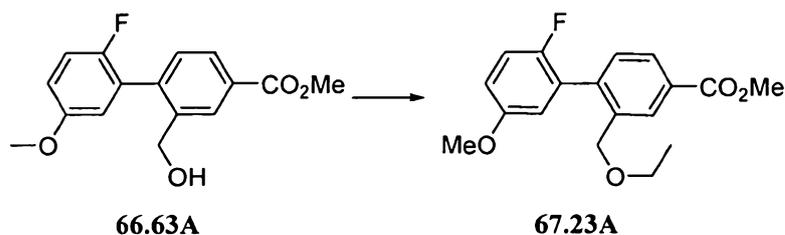
3.04 (1 H, m), 2.72 (4 H, m), 2.55 (2 H, m), 1.59 (2 H, m), 1.34 (6 H, m), 1.15 (2 H, m), 0.77 (3 H, t, J=7.2 Hz). MS ESI (pos.) m/e: 506.0 (M+H)⁺.

[0966] (3R)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.21).

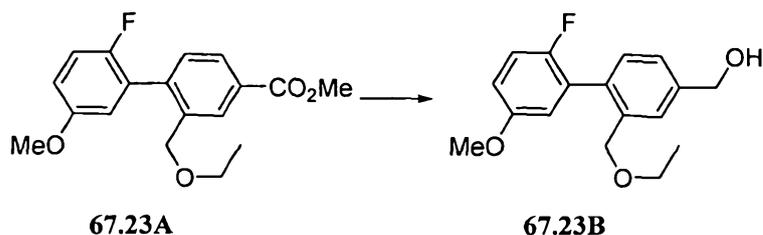
The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 43.6 (derived from peak one from the chiral separation of 43.4 from the OD-column) and 66.43I, described herein) to yield 67.21 (29.2 mg, 72% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.35 (1 H, d, J=7.4 Hz), 7.24 (1 H, t, J=8.0 Hz), 7.08 (1 H, d, J=10.6 Hz), 6.98 (1 H, t, J=9.0 Hz), 6.89 (5 H, m), 5.51 (1 H, m), 5.16 (2 H, s), 3.76 (3 H, s), 3.13 (1 H, m), 2.64 (2 H, ddd, J=18.0, 15.7, 7.4 Hz), 2.24 (2 H, td, J=7.0, 2.3 Hz), 1.68 (4 H, m), 1.24 (2 H, m), 0.90 (9 H, m). MS ESI (neg.) m/e: 532.9 (M-H)⁺.

[0967] (3R)-3-(3-(((4-(6-(Methoxy)-2-pyridinyl)phenyl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((4-(6-(methoxy)-2-pyridinyl)phenyl)methyl)oxy)phenyl)hexanoic acid (67.22). MS ESI (pos.) m/e: 462.3 (M+H)⁺.

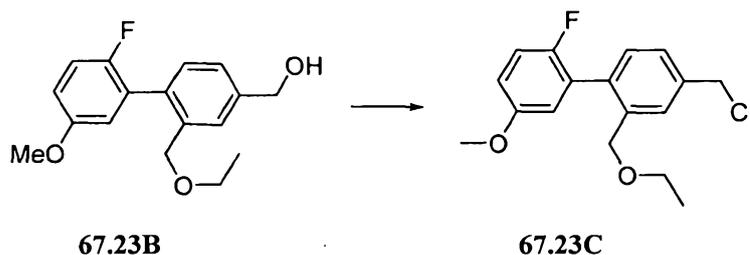
[0968] Example 67.23



[0969] Methyl 2-((ethoxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (67.23A). To a solution of 66.63A (0.200 g, 0.689 mmol) in DMF (5 mL), was added NaH (0.0198 g, 0.827 mmol). The reaction was stirred at room temperature for 10 minutes. Ethyl iodide was then added and the reaction was stirred at room temperatures for 1 hour. The mixture was diluted with EtOAc, washed with water and brine, and dried over anhydrous Na₂SO₄. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:1 EtOAc/hexane) and gave 67.23A in 79% yield. MS ESI (pos.) m/e: 336 (M+18)⁺.



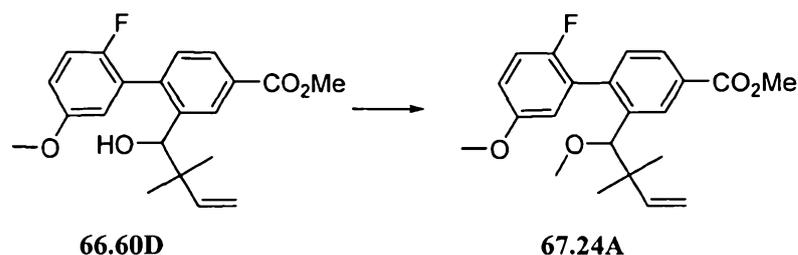
[0970] **(2-((Ethyloxy)methyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methanol (67.23B).** Example 67.23A was reduced using LAH using a procedure analogous to that of Example 66.6 to yield 67.23B.



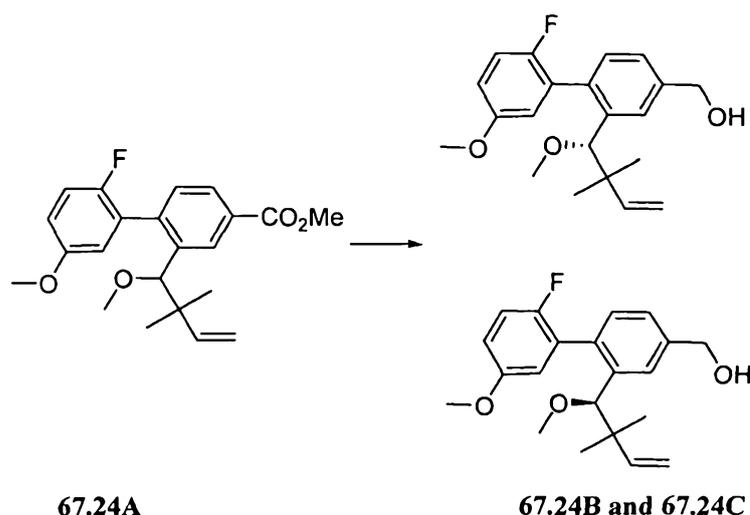
[0971] **4-(Chloromethyl)-2-((ethyloxy)methyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl (67.23C).** Compound 67.23B was converted to the chloromethyl compound using a procedure analogous to that described in Example 66.6.

[0972] **(3R)-3-(3-(((2-((Ethyloxy)methyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-((ethyloxy)methyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.23).** The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 43.6 (derived from peak one from the chiral separation of 43.4 from the OD-column) and 67.23C, described herein) to yield 67.23. MS ESI (neg.) m/e: 479 (M-H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.59 (m, 1H), 7.43-7.45 (m, 1H), 7.17-7.27 (m, 3H), 6.95-6.99 (m, 1H), 6.83-6.87 (m, 3H), 6.79 (m, 1H), 5.13 (s, 2H), 4.28 (s, 2H), 3.75 (s, 3H), 3.34 (m, 2H), 2.95 (m, 1H), 2.43-2.57 (m, 2H), 1.51 (m, 2H), 1.13 (m, 2H), 1.03 (t, 3H), 0.78 (t, 3H).

[0973] **Example 67.24**



[0974] **Methyl 2-(2,2-dimethyl-1-(methoxy)-3-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (67.24).** Compound 66.60D was alkylated using a procedure similar to that described in 66.62B to provide compound 67.24A.

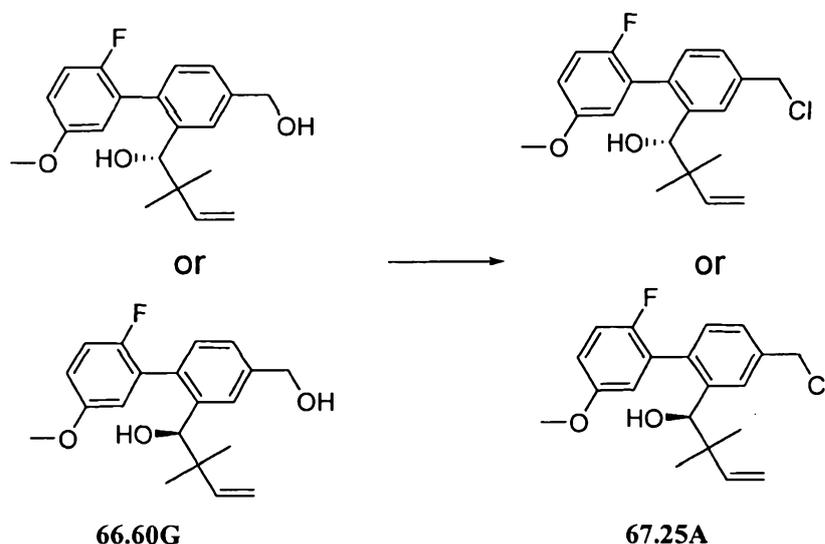


[0975] **(2-((1S)-2,2-Dimethyl-1-(methoxy)-3-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol and (2-((1R)-2,2-dimethyl-1-(methoxy)-3-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (67.24B and 67.24C).** To a solution of 67.24A (0.187 g, 0.52 mmol) in THF (10 mL), was added dropwise LAH (0.020 g, 0.52 mmol). The reaction was then stirred at room temperature for 10 minutes and then was carefully poured into water and extracted with EtOAc. The organic phase was dried over anhydrous Na₂SO₄. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:2 EtOAc / hexane) and gave the racemic product (168 mg) as a colorless oil, which was separated by chiral chromatography (column: OD; solvent: 3% i-PrOH / hexane) to yield 66.24B (70mg, first peak) and 66.24C (85mg, second peak).

[0976] **(3R)-3-(3-(((2-((1S)-2,2-Dimethyl-1-(methoxy)-3-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methoxy)phenyl)hexanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)-3-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-**

4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-((1S)-2,2-Dimethyl-1-(methoxy)-3-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)-3-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.24). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 43.6 (derived from peak one from the chiral separation of 43.4 from the OD-column) and 66.24B (derived from peak one from the chiral separation of the reduction product of 67.24A) to yield 67.24. MS ESI (neg.) m/e: 533 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.53 (m, 1H), 7.42-7.45 (m, 1H), 7.17-7.23 (m, 2H), 7.01-7.07 (m, 1H), 6.80-6.89 (m, 4H), 6.73-6.75 (m, 1H), 6.39(m, 2H), 5.75 (m, 1H), 5.14 (m, 2H), 3.81 (m, 2H), 3.07 (m, 3H), 3.09 (m, 1H), 2.13 (m, 2H), 1.62 (m, 2H), 1.29 (m, 6H), 1.21 (m, 2H), 0.87 (m, 3H).

[0977] **Example 67.25**

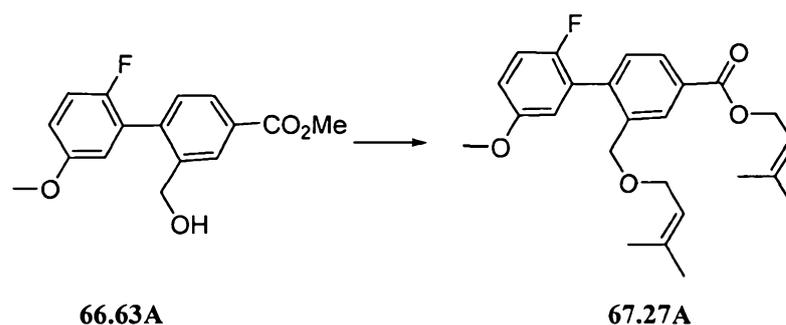


[0978] (1S)-1-(4-(Chloromethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-3-buten-1-ol or (1R)-1-(4-(chloromethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-3-buten-1-ol (67.25A). Hydroxymethyl compound 66.60G was chlorinated using a procedure analogous to that used to prepare Example 66.60H, (using peak two from the chiral separation of the reduction product of 66.60E from the OD-column, described herein) to yield 67.25A.

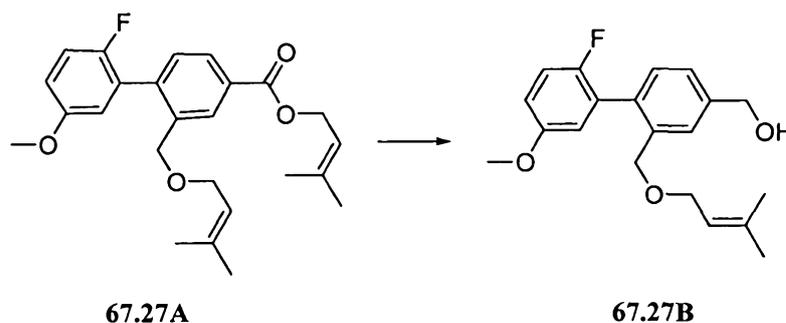
[0979] (3R)-3-(3-(((2'-Fluoro-2-((1S)-1-hydroxy-2,2-dimethyl-3-butenyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3R)-3-(3-(((2'-fluoro-2-((1R)-1-hydroxy-2,2-dimethyl-3-butenyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid **67.25**). The alkylation and hydrolysis were conducted in an analogous manner to Example **66.6** (using **43.6** (derived from peak one from the chiral separation of **43.4** from the OD-column) and **67.25A** (derived from peak two from the chiral separation of the reduction product of **66.60E**) to yield **67.25**. MS ESI (neg.) m/e: 519 (M-H). ¹H NMR (400 MHz, CD₃OD) δ ppm 7.69 (d, 1H), 7.39 (m, 1H), 7.05-7.25 (m, 3H), 6.94 (m, 1H), 6.79-6.84 (m, 4H), 5.78 (m, 1H), 5.14 (m, 2H), 4.71 (m, 2H), 3.79 (s, 3H), 3.03 (m, 1H), 2.52-2.58 (m, 2H), 1.59 (m, 2H), 1.16 (m, 2H), 0.82 (m, 6H), 0.72 (s, 3H).

[0980] (3R)-3-(3-(((2-((1S)-2,2-Dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (**67.26**). The alkylation and hydrolysis were conducted in an analogous manner to Example **66.6** (using **43.6** (derived from peak one from the chiral separation of **43.4** from the OD-column), also using the chloride derived from peak one from the chiral separation of the reduction product of **66.60E**, described herein) to yield **67.26**. MS ESI (neg.) m/e: 536 (M-H). ¹H NMR (400 MHz, CD₃OD) δ ppm 7.58 (m, 1H), 7.45 (m, 1H), 7.22 (m, 2H), 6.82-6.88 (m, 4H), 6.74 (m, 1H), 5.15 (s, 2H), 4.05-4.30 (m, 1H), 3.23-3.29 (m, 3H), 3.08 (m, 1H), 2.61-2.65 (m, 2H), 1.62 (m, 2H), 1.10-1.27 (m, 4H), 0.86 (t, 3H), 0.72 (s, 3H), 0.61 (m, 3H), 0.49 (m, 3H).

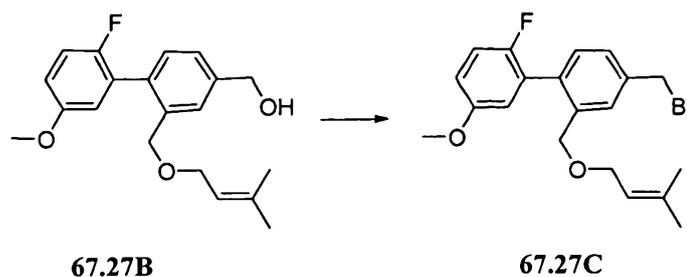
[0981] Example 67.27



[0982] **3-Methyl-2-butenyl 2'-fluoro-2-(((3-methyl-2-butenyl)oxy)methyl)-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (67.27A).** To a solution of **66.63A** (0.322 mmol) in DMF (4 mL), was added NaH (0.0100 g, 0.419 mmol). The resulting mixture was stirred at room temperature for 10 minutes. 1-Bromo-3-methylbut-2-ene (0.240 g, 1.61 mmol)(commercially available from Aldrich) was added and the mixture was stirred at room temperature for 2 hours. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:6 EtOAc / hexane) and gave **67.27A** as a colorless oil, in 77% yield. MS ESI (pos.) m/e: 430 (M+18)⁺.



[0983] **(2'-Fluoro-2-(((3-methyl-2-butenyl)oxy)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (67.27B).** The conversion of ester **67.27A** to hydroxymethyl compound **67.27B** was conducted using a procedure analogous to that described in Example **66.63D**.



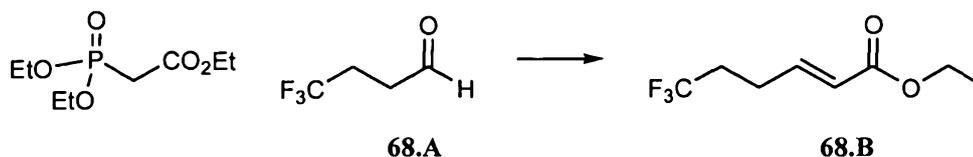
[0984] **4-(Bromomethyl)-2'-fluoro-2-(((3-methyl-2-butenyl)oxy)methyl)-5'-(methoxy)-1,1'-biphenyl (67.27C)**. Hydroxymethyl compound **67.2B** was converted to bromomethyl **67.27C** using a procedure analogous to that of Example **66.62E**.

[0985] **(3R)-3-(3-(((2'-Fluoro-2-(((3-methyl-2-butenyl)oxy)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2'-fluoro-2-(((3-methyl-2-butenyl)oxy)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.27)**. The alkylation and hydrolysis were conducted in an analogous manner to Example **66.6** (using **43.6** (derived from peak one from the chiral separation of **43.4** from the OD-column) and **67.27C**) to yield **67.27**. MS ESI (neg.) m/e: 519 (M-H). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.59 (m, 1H), 7.42 (m, 1H), 7.21-7.29 (m, 2H), 7.02-7.07 (m, 1H), 6.80-6.87 (m, 5H), 5.23 (m, 1H), 5.15 (s, 2H), 4.37 (s, 2H), 3.92 (d, 3H), 3.06 (m, 1H), 2.52-2.65 (m, 2H), 1.70 (m, 3H), 1.62 (m, 2H), 1.58 (s, 3H), 1.21 (m, 2H), 0.87 (t, 3H).

[0986] **(3R)-3-(3-(((2'-Fluoro-5'-(methoxy)-2-(1-pyrrolidinylmethyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2'-fluoro-5'-(methoxy)-2-(1-pyrrolidinylmethyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (67.28)**. The alkylation and hydrolysis were conducted in an analogous manner to Example **66.6** (using **43.6** (derived from peak one from the chiral separation of **43.4** from the OD-column) and **66.65C**) to yield **67.28**. After removing solvent, **67.28** (TFA salt), 28mg, was obtained. MS ESI (neg.) m/e: 504 (M-H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.70(m, 1H), 7.84 (s, 1H), 7.60 (m, 1H), 7.39 (m, 1H), 7.21-7.30 (m, 2H), 7.05-7.07 (m, 1H), 6.3-6.95 (m, 1H), 6.88 (m, 2H), 6.83 (m, 1H), 5.17 (s, 2H), 4.10-4.40 (m, 2H), 3.79 (s, 3H), 3.40-3.60 (m, 4H), 2.97 (m, 1H), 2.42-2.55 (m, 2H), 1.80 (m, 4H), 1.51 (m, 2H), 1.06 (m, 2H), 0.80 (t, 3H).

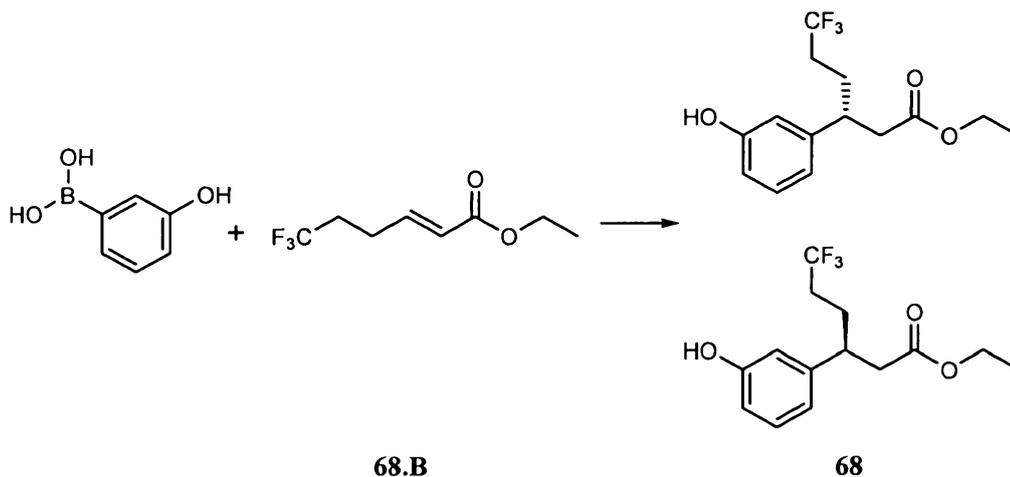
[0987] **Example 68**

[0988] **Synthesis of methyl (3R)-6,6,6-trifluoro-3-(3-hydroxyphenyl)hexanoate (68)**.



[0989] **(E)-Ethyl 6,6,6-trifluorohex-2-enoate (68.B)**. To a suspension of lithium chloride (0.504 g, 11.9 mmol) in MeCN (20 mL) were added ethyl 2-

(diethoxyphosphoryl)acetate (available from Aldrich)(1.91 mL, 9.52 mmol) and DBU (1.42 mL, 9.52 mmol) at room temperature. The mixture was cooled to 0°C, and 4,4,4-trifluorobutanal (available from Matrix Scientific)(1.00 g, 7.93 mmol) was added dropwise. The resulting mixture was warmed to room temperature and stirred overnight. The mixture was partitioned between water and EtOAc. The layers were separated, and the aqueous phase was extracted with additional EtOAc. The combined organic layers were washed with water and brine, dried (MgSO₄), and concentrated. The residue was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to afford (E)-ethyl 6,6,6-trifluorohex-2-enoate **68.B** (6:1 E/Z) as a colorless liquid (1.13g, 73%).

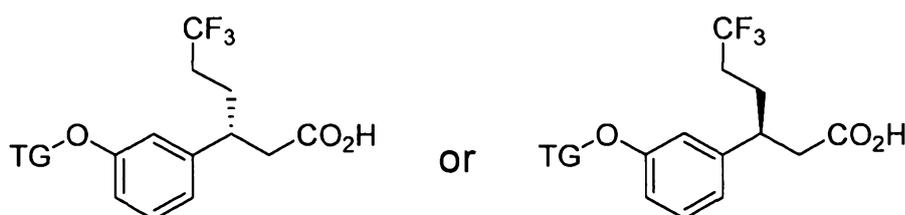


[0990] Methyl (3R)-6,6,6-trifluoro-3-(3-hydroxyphenyl)hexanoate or methyl (3S)-6,6,6-trifluoro-3-(3-hydroxyphenyl)hexanoate (68). A mixture of 3-hydroxyphenylboronic acid (available from Aldrich)(1.8 g, 13 mmol) and hydroxy[(S)-BINAP]-rhodium(I) dimer (0.19 g, 0.13 mmol) in 1,4-dioxane (10 mL, 2.5 mmol) was sparged with N₂. To the mixture were added water (1.0 mL, 2.5 mmol) and (E)-ethyl 6,6,6-trifluorohex-2-enoate **68.B** (0.56 mL, 2.5 mmol). The resulting red-brown solution was warmed to 45°C and stirred for 3 hours (sealed vial). The mixture was cooled to room temperature, diluted with EtOAc, washed with saturated aqueous NaHCO₃ and brine, dried (MgSO₄), and concentrated. The residue was purified by silica gel flash chromatography (0-25% EtOAc/hexane) to afford (R)-ethyl 6,6,6-trifluoro-3-(3-hydroxyphenyl)hexanoate and (S)-ethyl 6,6,6-trifluoro-3-(3-hydroxyphenyl)hexanoate **68** as a pale yellow oil (84% e.e.). The enantiomerically enriched mixture was further purified by chiral HPLC (Chiralcel OD, 3% i-PrOH/hexane, 220 nm) to afford **68** as a

colorless oil (0.65 g, > 99% e.e.). The R enantiomer is believed to be the major product used in the following steps.

[0991] The following compounds were prepared from 68 and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Both of the compounds in the following table were prepared using the same enantiomer of the phenol.

Table 8



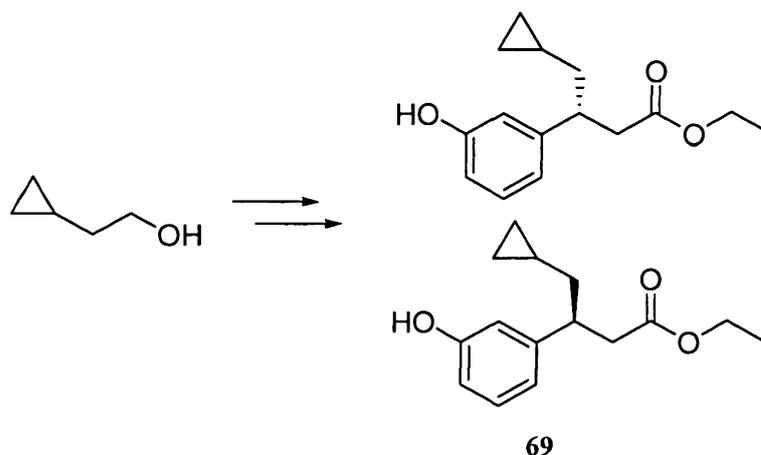
Compound	TG	Compound	TG
68.1		68.2	

[0992] (3R)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-6,6,6-trifluorohexanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-6,6,6-trifluorohexanoic acid (68.1). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.60 (d, 1H), 7.28 (m, 2H), 7.05 (d, 1H), 6.99 (t, 1H), 6.91 (dd, 1H), 6.84 (m, 2H), 6.80 (bd, 1H), 6.77 (dd, 1H), 5.07 (s, 2H), 3.78 (s, 3H), 3.10 (m, 1H), 2.67 (m, 2H), 1.91 (m, 4H), 1.23 (s, 9H).

[0993] (3R)-3-(3-(((2-(Butyloxy)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-6,6,6-trifluorohexanoic acid or (3S)-3-(3-(((2-(butyloxy)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-6,6,6-trifluorohexanoic acid (68.2). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.29 (d, 1H), 7.26 (t, 1H), 7.06 (m, 2H), 7.02 (t, 1H), 6.89 (m, 2H), 6.82 (m, 3H), 5.07 (s, 2H), 3.99 (t, 2H), 3.79 (s, 3H), 3.09 (m, 1H), 2.67 (m, 2H), 1.91 (m, 4H), 1.66 (m, 2H), 1.37 (m, 2H), 0.88 (t, 3H).

[0994] **Example 69**

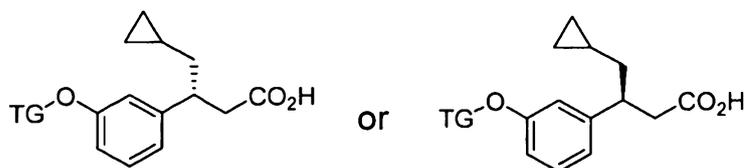
[0995] Synthesis of (R)-ethyl 4-cyclopropyl-3-(3-hydroxyphenyl)butanoate or (S)-ethyl 4-cyclopropyl-3-(3-hydroxyphenyl)butanoate (69).



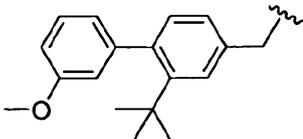
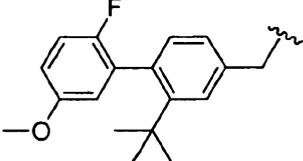
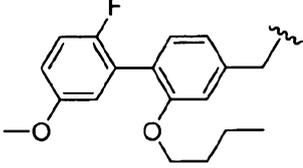
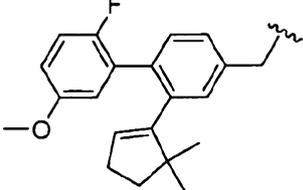
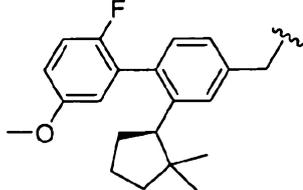
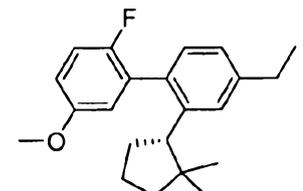
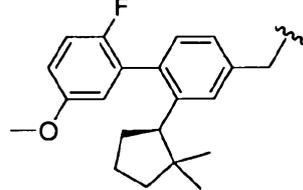
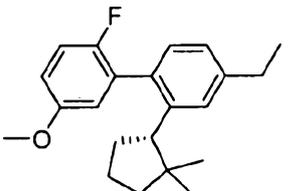
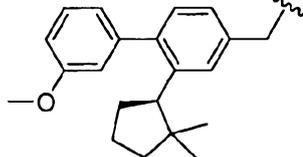
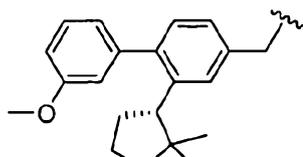
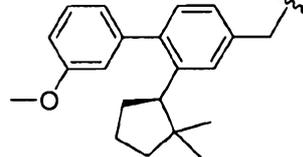
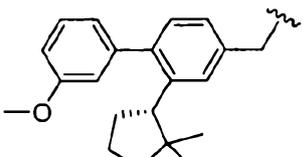
[0996] (R)-Ethyl 4-cyclopropyl-3-(3-hydroxyphenyl)butanoate and (S)-Ethyl 4-cyclopropyl-3-(3-hydroxyphenyl)butanoate (69). Compound **69** (99% e.e.) was prepared from 2-cyclopropylethanol (commercially available from Alfa Aesar) according to the analogous methods described in Example 70. The final chiral resolution was achieved by chiral HPLC (Chiralcel OD column, 3% IPA/hexane, detection at 220 nm) to afford **69** as the first of two eluted peaks. This is believed to be the R enantiomer.

[0997] The following compounds were prepared from **69** and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Each of the compounds in the following table were prepared using the same enantiomer of the phenol.

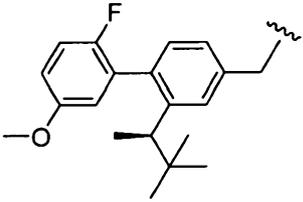
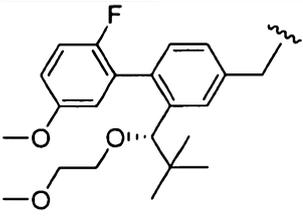
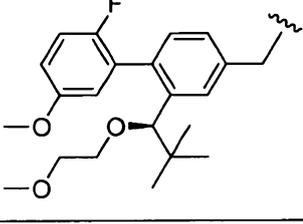
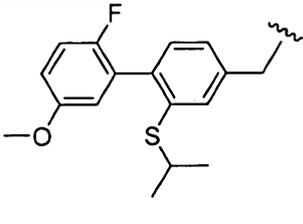
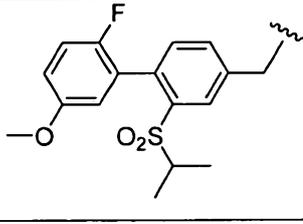
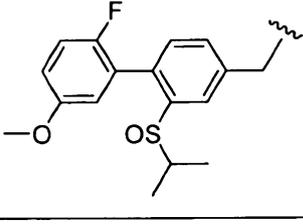
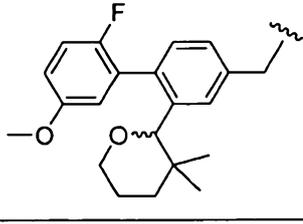
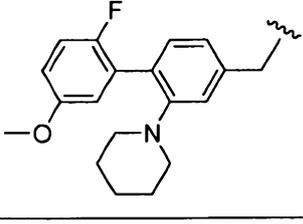
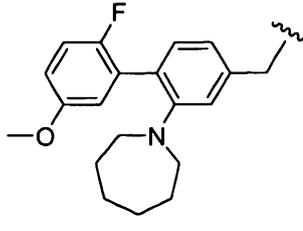
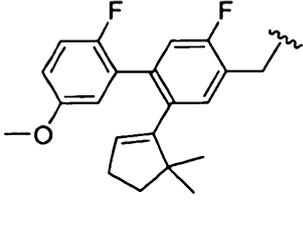
Table 9

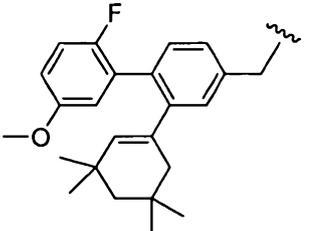
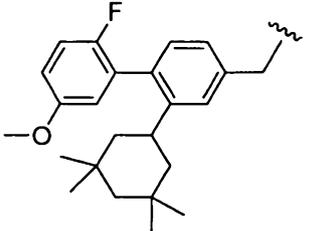
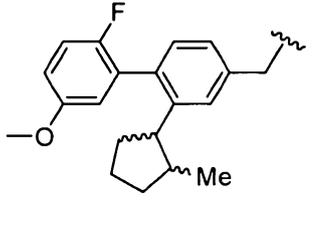
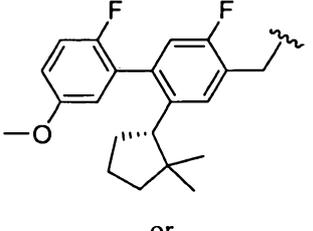
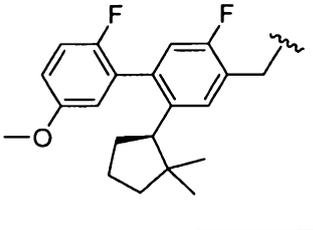
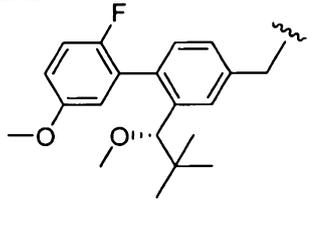
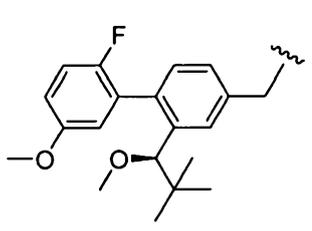
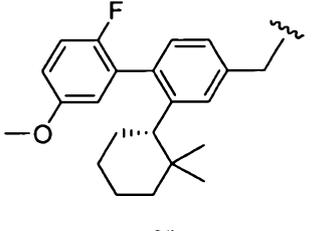
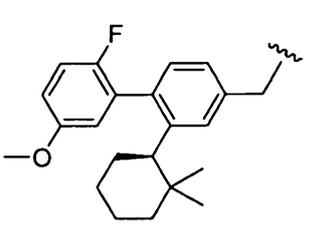
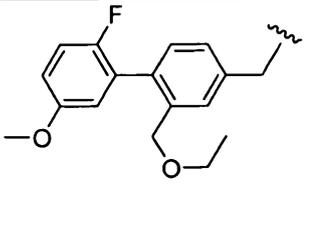
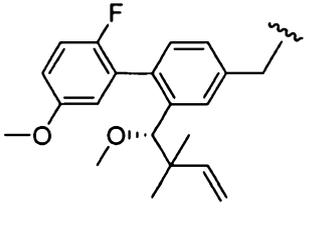


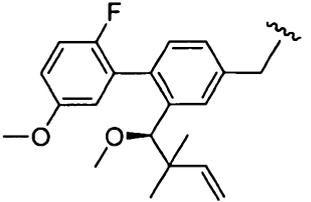
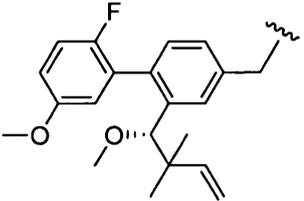
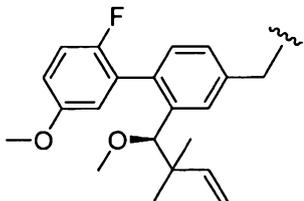
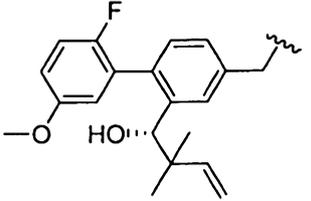
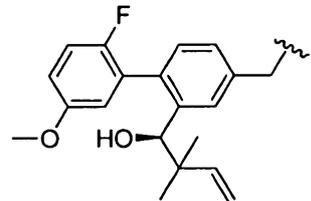
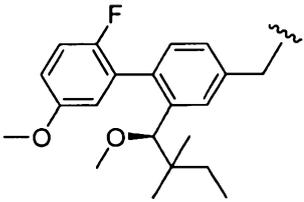
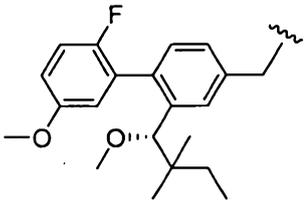
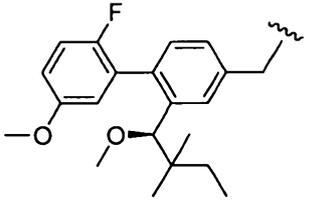
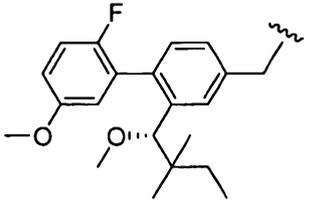
Compound	TG	Compound	TG
69.1		69.2	

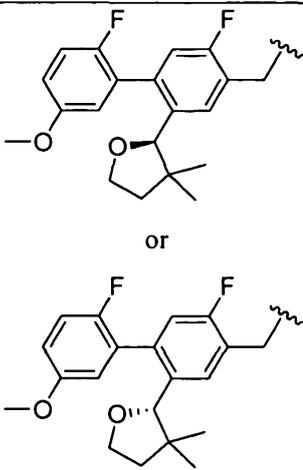
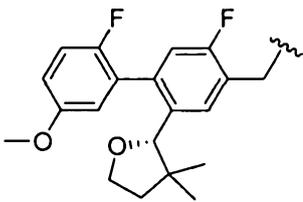
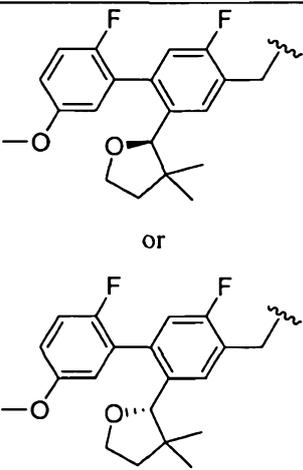
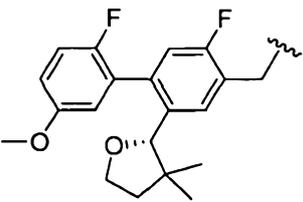
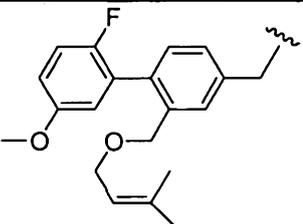
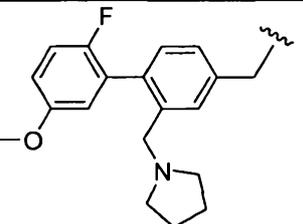
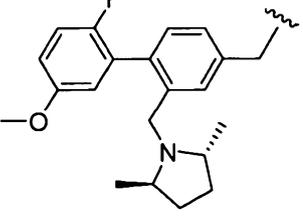
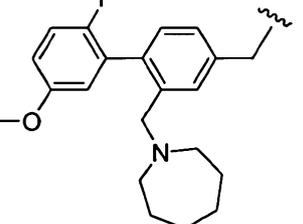
Compound	TG	Compound	TG
69.3		69.4	
69.5		69.6	
69.7	 <p data-bbox="644 1037 676 1059">or</p> 	69.8	 <p data-bbox="1166 1037 1198 1059">or</p>  <p data-bbox="1023 1305 1310 1384">but not the same one as 69.7</p>
69.9	 <p data-bbox="644 1597 676 1619">or</p> 	69.10	 <p data-bbox="1166 1597 1198 1619">or</p>  <p data-bbox="1023 1832 1310 1910">but not the same one as 69.9</p>

Compound	TG	Compound	TG
69.11		69.12	
69.13		69.14	
69.15		69.16	
69.17		69.18	
69.19		69.20	
69.21		69.22	

Compound	TG	Compound	TG
			
69.23	 <p style="text-align: center;">or</p> 	69.24	
69.25		69.26	
69.27		69.28	
69.29		69.30	

Compound	TG	Compound	TG
69.31		69.32	
69.33		69.34	 or 
69.35	 or 	69.36	 or 
69.37		69.38	 or 

Compound	TG	Compound	TG
			
<p>69.39</p>	 <p>or</p>  <p>but not the same one as 69.38</p>	<p>69.40</p>	 <p>or</p> 
<p>69.41</p>	 <p>or</p> 	<p>69.42</p>	 <p>or</p>  <p>but not the same one as 69.41</p>

Compound	TG	Compound	TG
69.43	 <p>or</p> 	69.44	 <p>or</p>  <p>but not the same one as 69.43</p>
69.45		69.46	
69.47		69.48	

[0998] (3R)-3-(3-(((2-Cycloheptyl-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-cyclopropylbutanoic acid or (3S)-3-(3-(((2-cycloheptyl-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-cyclopropylbutanoic acid (69.1). MS ESI (neg.) m/e: 529.3 (M-H)⁺.

[0999] (3R)-4-Cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.2). MS ESI (neg.) m/e: 509.2 (M-H)⁺.

[01000] (3R)-4-Cyclopropyl-3-(3-(((2-(1,1-dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-(1,1-dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.3). (MS ESI (neg.) m/e: 471.3 (M-H). ¹H NMR (400 MHz) (CDCl₃) δ ppm 7.55 (1 H, d, J=1.6 Hz), 7.25 (3 H, m), 7.02 (1 H, d, J=7.4 Hz), 6.85 (5 H, dt, J=5.5, 2.7 Hz), 6.81 (1 H, s), 5.04 (2 H, s), 3.78 (3 H, s), 3.23 (1 H, m), 2.75 (1 H, m), 2.66 (1 H, m), 1.68 (1 H, ddd, J=13.9, 8.4, 5.9 Hz), 1.37 (1 H, m), 1.20 (9 H, s), 0.55 (1 H, m), 0.39 (2 H, m), 0.04 (2 H, m).

[01001] (3R)-4-Cyclopropyl-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.4). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.60 (dd, 1H), 7.29 (dd, 1H), 7.24 (t, 1H), 7.04 (d, 1H), 6.99 (t, 1H), 6.86 (m, 4H), 6.77 (dd, 1H), 5.07 (s, 2H), 3.78 (s, 3H), 3.21 (m, 1H), 2.75 (dd, 1H), 2.64 (dd, 1H), 1.71 (m, 1H), 1.34 (m, 1H), 1.23 (s, 9H), 0.52 (m, 1H), 0.36 (m, 2H), 0.00 (m, 2H).

[01002] (3R)-3-(3-(((2-(Butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-cyclopropylbutanoic acid or (3S)-3-(3-(((2-(butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-cyclopropylbutanoic acid (69.5). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.28 (d, 1H), 7.23 (t, 1H), 7.06 (m, 2H), 7.02 (t, 1H), 6.85 (m, 5H), 5.07 (s, 2H), 3.98 (t, 2H), 3.79 (s, 3H), 3.21 (m, 1H), 2.75 (dd, 1H), 2.64 (dd, 1H), 1.70 (m, 1H), 1.66 (m, 2H), 1.36 (m, 3H), 0.88 (t, 3H), 0.52 (m, 1H), 0.36 (m, 2H), 0.00 (m, 2H).

[01003] (3R)-4-Cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.6). MS ESI (pos.) m/e: 546.3 (M+H₂O)⁺.

[01004] (3R)-4-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-

dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-

yl)methyl)oxy)phenyl)butanoic acid (69.7). MS ESI (neg.) m/e: 529.3 (M-H)⁺.

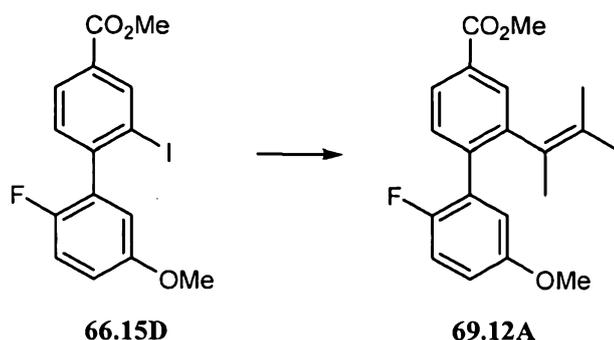
[01005] (3R)-4-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.8). MS ESI (neg.) m/e: 529.3 (M-H)⁺.

[01006] (3R)-4-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.9). MS ESI (neg.) m/e: 511.3 (M-H)⁺.

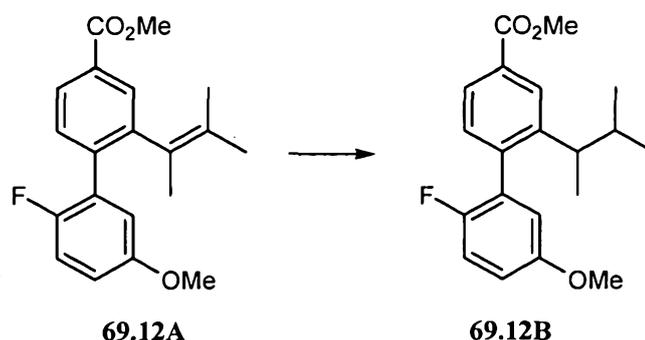
[01007] (3R)-4-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.10). MS ESI (neg.) m/e: 511.3 (M-H)⁺.

[01008] (3R)-3-(3-(((2-Cycloheptyl-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-cyclopropylbutanoic acid or (3S)-3-(3-(((2-cycloheptyl-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-cyclopropylbutanoic acid (69.11). MS ESI (neg.) m/e: 511.3 (M-H)⁺.

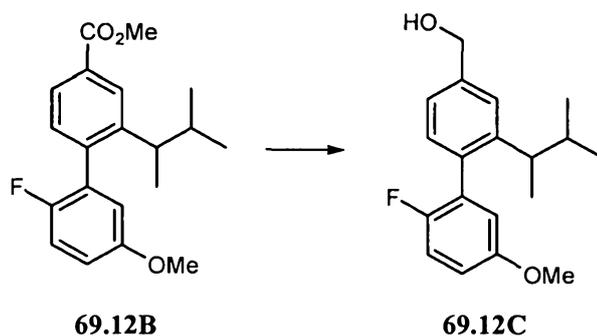
[01009] Example 69.12



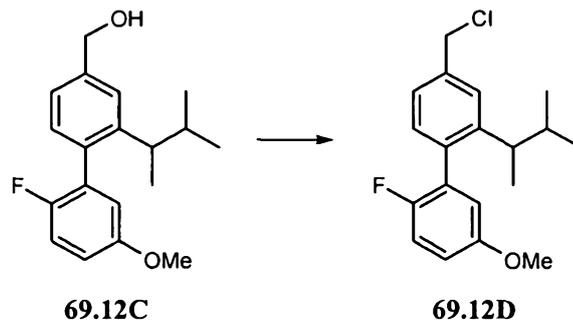
[01010] **Methyl 2-(1,2-dimethyl-1-propenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (69.12A).** To a stirred solution of **66.15D** (0.231 g, 0.60 mmol) in DMF (4.00 mL) at 23°C was added 3-methylbut-2-en-2-ylboronic acid (0.14 g, 1.2 mmol, commercially available from Aldrich), and potassium carbonate (0.25 g, 1.8 mmol). Tetrakis(triphenylphosphine)palladium (0.069 g, 0.060 mmol) was then added to the reaction. The mixture was heated to 90°C and stirring was continued for 18 hours. The reaction was then cooled to room temperature, diluted with water and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **69.12A** as a colorless oil (0.100 g, 51% yield).



[01011] **Methyl 2-(1,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (69.12B).** To a stirred solution of **69.12A** (0.050 g, 0.2 mmol) in EtOAc (3 mL) at 23°C was added palladium on carbon (0.02 g, 0.2 mmol). The reaction was placed under an atmosphere of hydrogen and stirred for four hours. The reaction was then filtered and concentrated in vacuo. The purity of **69.12B** was deemed sufficient such that it was used directly in the next reaction.



[01012] **(2-(1,2-Dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (69.12C)**. To a stirred solution of **69.12B** (0.050 g, 0.2 mmol) in THF (3 mL) at 0°C was added LAH (0.3 mL, 0.3 mmol, 1.0M). The reaction was stirred for one hour and then 1N NaOH(aq) was added to the mixture. The reaction was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was purified on silica gel (0-20% EtOAc in hexanes) to yield **69.12C** as a colorless oil (0.011 g, 24% yield).



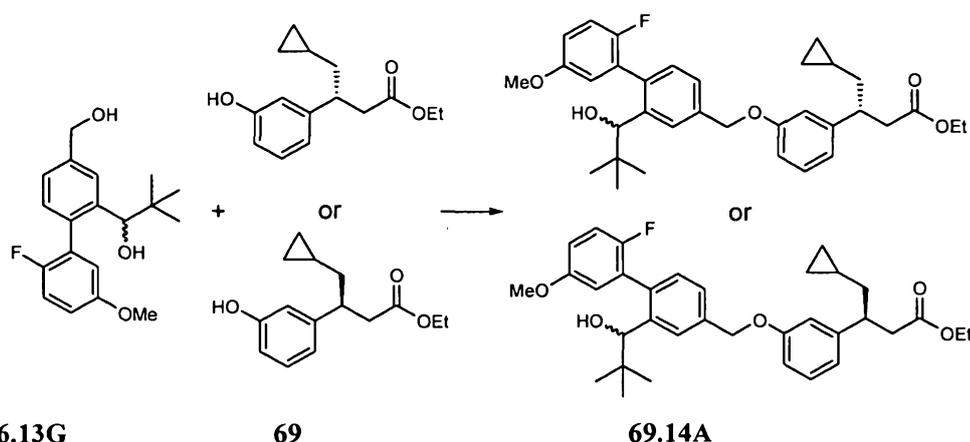
[01013] **4-(Chloromethyl)-2-(1,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (69.12D)**. To a stirred solution of **69.12C** (0.011 g, 0.04 mmol) in DCM (2.00 mL) and DMF (0.003 mL) at 0°C was added thionyl chloride (0.005 mL, 0.07 mmol). The reaction was then stirred at room temperature for two hours, concentrated in vacuo, and the chloride **69.12D** was used crude without further purification (0.011 g, 94% yield).

[01014] **(3R)-4-Cyclopropyl-3-(3-(((2-(1,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-(1,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid 69.12**. The alkylation and hydrolysis were

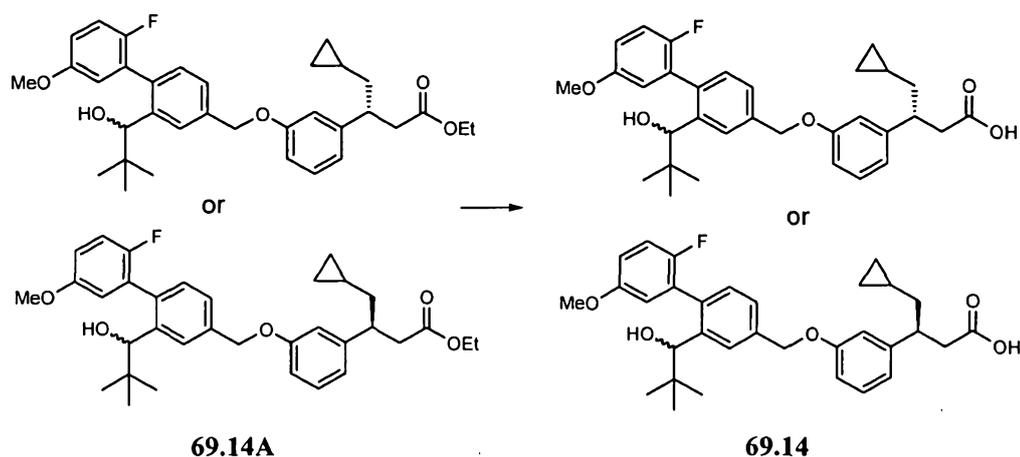
conducted in an analogous manner to Example 66.6 using 69.12D and 69 to yield 69.12 (0.0104 g, 52% yield over two steps). MS ESI (neg.) m/e: 503.2 (M-H)⁺.

[01015] (3R)-3-(3-(((2-Cyclooctyl-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-cyclopropylbutanoic acid or (3S)-3-(3-(((2-cyclooctyl-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-cyclopropylbutanoic acid (69.13). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 using 66.16G and 69 to yield 69.13 (0.021 g, 63% yield over two steps). MS ESI (neg.) m/e: 543.2 (M-H)⁺.

[01016] **Example 69.14**

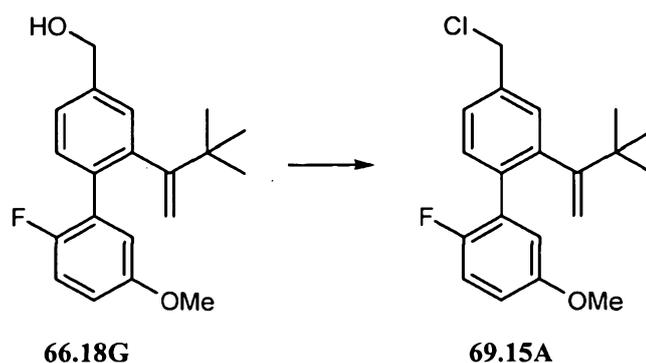


[01017] Ethyl (3R)-4-cyclopropyl-3-(3-(((2'-fluoro-2-(1-hydroxy-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate or ethyl (3S)-4-cyclopropyl-3-(3-(((2'-fluoro-2-(1-hydroxy-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate (69.14A). To a stirred solution of 69 (0.078 g, 0.31 mmol) in THF (2.00 mL, 24 mmol) at 23°C was added 66.13G (0.050 g, 0.16 mmol) followed by triphenylphosphine (0.082 g, 0.31 mmol) and diethyl azodicarboxylate (0.049 mL, 0.31 mmol). The reaction was then stirred for 23 hours, diluted with water, and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield 69.14A as a colorless oil (0.045 g, 52% yield).



[01018] **(3R)-4-Cyclopropyl-3-(3-(((2'-fluoro-2-(1-hydroxy-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2'-fluoro-2-(1-hydroxy-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.14).** The hydrolysis was conducted in an analogous manner to Example 66.6 using 69.14A to yield 69.14 (0.014 g, 98% yield). MS ESI (neg.) m/e: 519.2 (M-H)⁺.

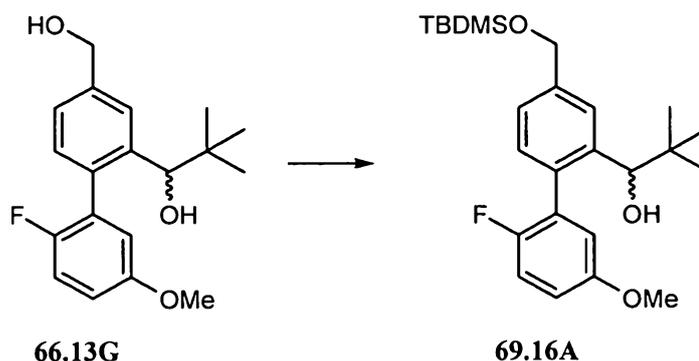
[01019] **Example 69.15**



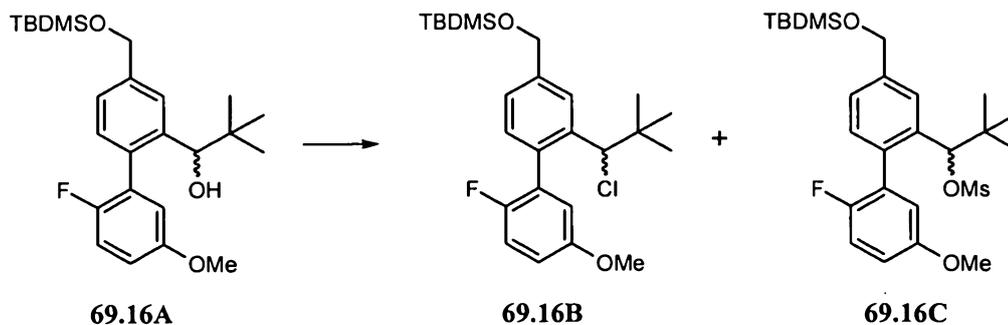
[01020] **4-(Chloromethyl)-2-(1-(1,1-dimethylethyl)ethenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (69.15A).** To a stirred solution of 66.18F (0.050 g, 0.16 mmol) in DCM (2.00 mL) at 0°C was added DMF (0.0012 mL), followed by thionyl chloride (0.023 mL, 0.32 mmol). The reaction was then stirred for 1.5 hours and then concentrated in vacuo. The product was purified on silica gel (0-10% EtOAc in hexanes) to yield 69.15A as a colorless oil (0.050 g, 94% yield).

[01021] (3R)-4-Cyclopropyl-3-(3-(((2-(1-(1,1-dimethylethyl)ethenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-(1-(1,1-dimethylethyl)ethenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.15). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 using 69.15A and 69 to yield 69.15 (0.0342 g, 90% yield over two steps). MS ESI (neg.) m/e: 515.2 (M-H)⁺.

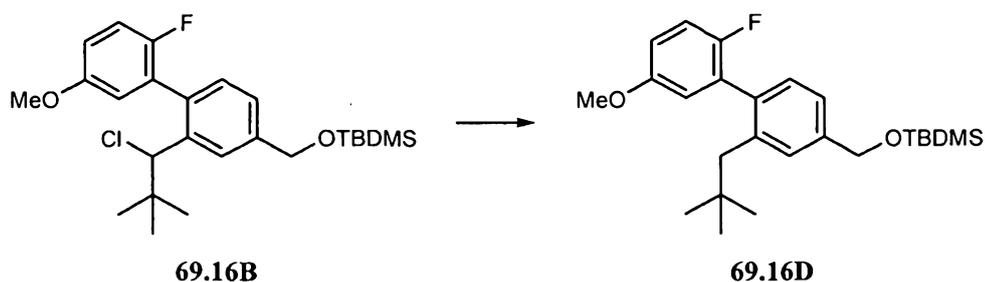
[01022] **Example 69.16**



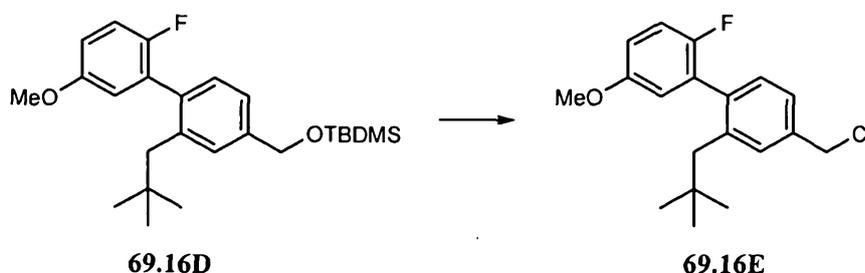
[01023] 1-(4-(((1,1-Dimethylethyl)(dimethyl)silyl)oxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol (69.16A). To a stirred solution of 66.13G (0.500 g, 2 mmol) in DCM (10.00 mL) at 23°C was added tert-butyldimethylsilyl chloride (0.3 mL, 2 mmol), followed by TEA (0.3 mL, 2 mmol) and DMAP (0.02 g, 0.2 mmol). The reaction was then stirred for 16 hours and concentrated in vacuo. The product was purified on silica gel (0-10% EtOAc in hexanes) to yield 69.16A as a colorless oil (0.655 g, 96% yield).



[01024] **(((2-(1-Chloro-2,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)(1,1-dimethylethyl)dimethylsilane (69.16B)**. To a stirred solution of **69.16A** (0.200 g, 0.46 mmol) in DCM (5.00 mL) at 0°C was added TEA (0.077 mL, 0.55 mmol), followed by methanesulfonyl chloride (0.043 mL, 0.55 mmol). The reaction was then stirred for 22 hours, diluted with water, and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was purified on silica gel (0-10% EtOAc in hexanes) to yield **69.16B** as a colorless oil (0.090 g, 43% yield) and a further product **69.16C** as a clear oil (0.050 g, 21% yield).



[01025] **(1,1-Dimethylethyl) (((2-(2,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)dimethylsilane (69.16D)**. To a stirred solution of **69.16B** (0.015 g, 0.033 mmol) in toluene (2.00 mL) at 23°C was added AIBN (0.00055 g, 0.0033 mmol) followed by tri-n-butyltin hydride (0.048 g, 0.17 mmol). The reaction was stirred at 100°C for two hours. After which, the reaction was cooled to room temperature and concentrated in vacuo. The product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **69.16D** as a colorless oil (0.013 g, 94% yield).

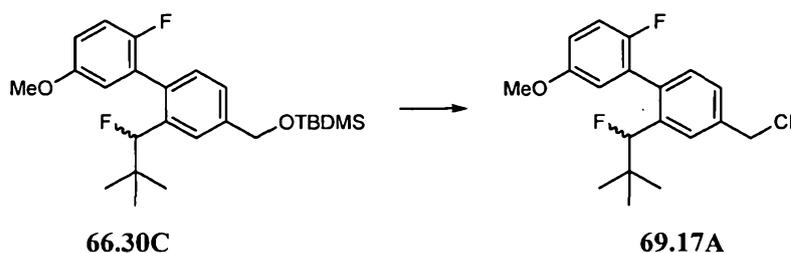


[01026] **4-(Chloromethyl)-2-(2,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (69.16E)**. The chlorination was conducted in an analogous manner to that

employed in Example 66.6 using 69.16D (described here within) to yield chloride 69.16E.

[01027] (3R)-4-Cyclopropyl-3-(3-(((2-(2,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-(2,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.16). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 using 69.16E and 69 to yield 69.16 (0.0286 g, 70% yield over two steps). MS ESI (neg.) m/e: 503.2 (M-H)⁺.

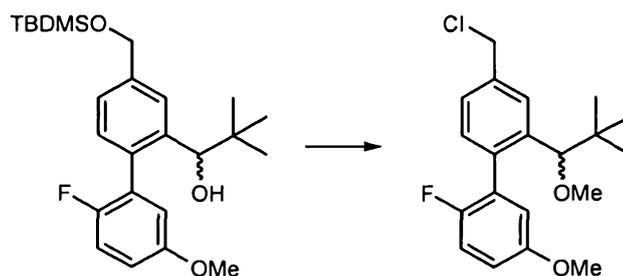
[01028] **Example 69.17**



[01029] 4-(Chloromethyl)-2'-fluoro-2-(1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl (69.17A). The chlorination of Example 66.30C was conducted in an analogous manner to that employed in Example 66.6 using 66.30C to yield chloride 69.17A..

[01030] (3R)-4-cyclopropyl-3-(3-(((2'-fluoro-2-(1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2'-fluoro-2-(1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.17). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 using 69.17A and 69 to yield 69.17 (0.0294 g, 70% yield over two steps). MS ESI (neg.) m/e: 521.2 (M-H)⁺.

[01031] **Example 69.18**

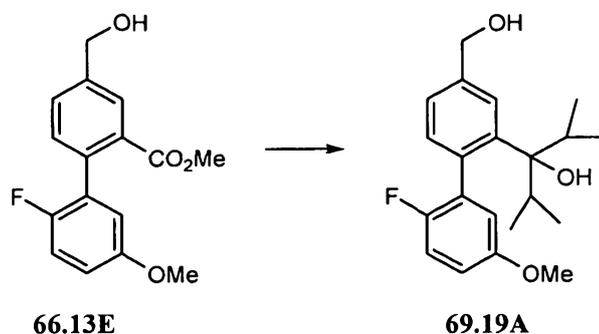


69.16A

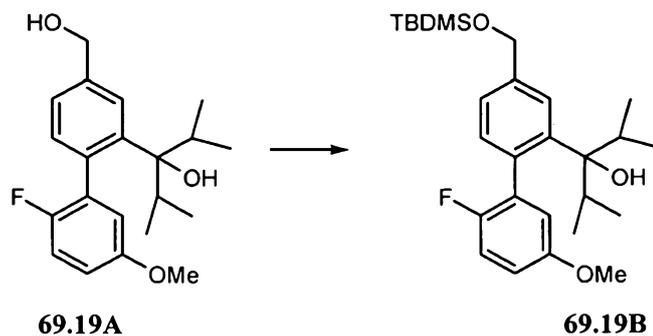
69.18A

[01032] 4-(Chloromethyl)-2-(2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (69.18B). The alkylation and chlorination were conducted in an analogous manner to that employed in Example 66.13 using 69.16A to yield chloride 69.18A.

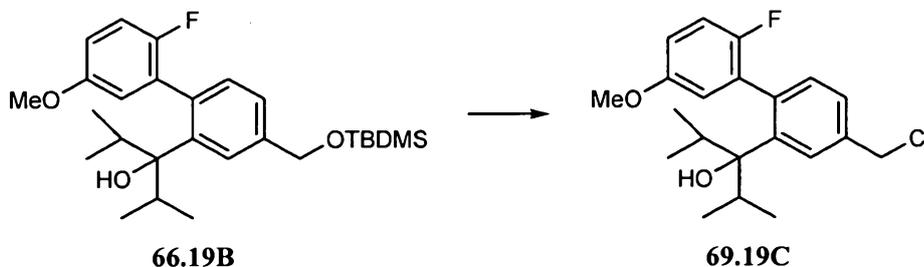
[01033] (3R)-4-Cyclopropyl-3-(3-(((2-(2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-(2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.18). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 using 69.18A and 69 to yield 69.18 (0.0297 g, 69% yield over two steps). MS ESI (neg.) m/e: 533.2 (M-H)⁻.

[01034] Example 69.19

[01035] 3-(2'-Fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,4-dimethyl-3-pentanol (69.19A). To a stirred solution of 66.13E (0.500 g, 1.7 mmol) in THF (17 mL, 1.7 mmol) at -78°C was added isopropylolithium (8.6 mL, 6.0 mmol). The reaction was allowed to warm to room temperature and stirred for 22 hours. The reaction was then diluted with a saturated solution of ammonium chloride and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield 69.19A as a yellow oil (0.450 g, 75% yield).



[01036] **3-(4-(((1,1-Dimethylethyl)(dimethyl)silyl)oxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,4-dimethyl-3-pentanol (69.19B)**. To a stirred solution of **66.19A** (0.500 g, 1 mmol) in DCM (10.00 mL) at 23°C was added tert-butyldimethylsilyl chloride (0.3 mL, 2 mmol), followed by TEA (0.2 mL, 2 mmol) and DMAP (0.02 g, 0.1 mmol). The reaction was then stirred for 2.5 hours and then concentrated in vacuo. The product was purified on silica gel (0-10% EtOAc in hexanes) to yield **69.19B** as a colorless oil (0.600 g, 90% yield).



[01037] **3-(4-(Chloromethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-2,4-dimethyl-3-pentanol (69.19C)**. To a stirred solution of **69.19B** (0.050 g, 0.1 mmol) in DCM (2.00 mL) at 23°C was added DMF (0.0008 mL) followed by thionyl chloride (0.01 mL, 0.2 mmol). The reaction was then stirred for 1.5 hours and then concentrated in vacuo. The product was purified on silica gel (0-10% EtOAc in hexanes) to yield **69.19C** as a colorless oil (0.04 g, 100% yield).

[01038] **(3R)-4-Cyclopropyl-3-(3-(((2'-fluoro-2-(1-hydroxy-2-methyl-1-(1-methylethyl)propyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2'-fluoro-2-(1-hydroxy-2-methyl-1-(1-methylethyl)propyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.19)**. The alkylation and hydrolysis were conducted in an analogous manner to

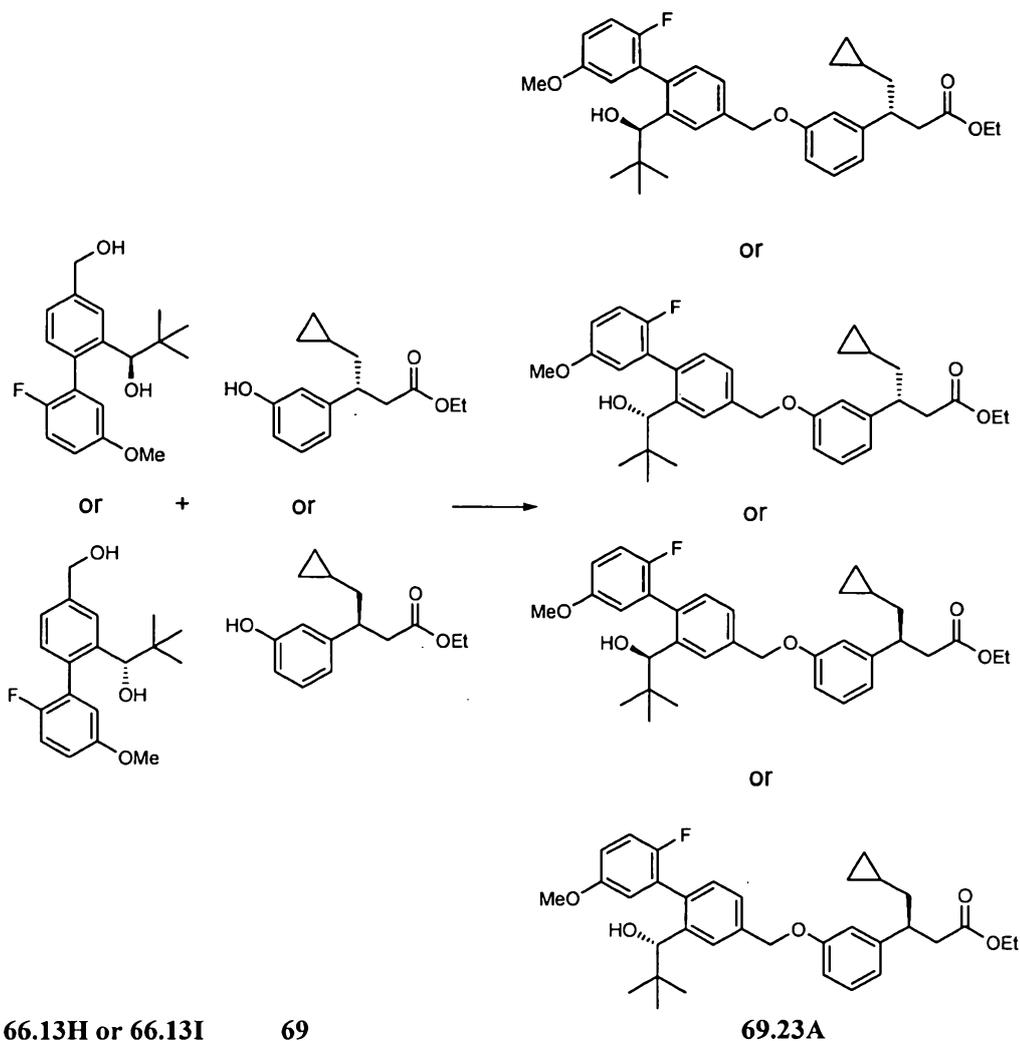
Example 66.6 using 69.19C and 69 to yield 69.19 (0.0236 g, 71% yield over two steps). MS ESI (neg.) m/e: 547.3 (M-H)⁺.

[01039] (3R)-4-Cyclopropyl-3-(3-(((2-(2,2-dimethylpropanoyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-(2,2-dimethylpropanoyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.20). The Mitsunobu reaction and hydrolysis were conducted in an analogous manner to Example 26.5 (Mitsunobu) and 66.6 (hydrolysis) using 66.13F and 69 to yield 69.20. MS ESI (neg.) m/e: 517.3 (M-H)⁺.

[01040] (3R)-4-Cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-(2-methylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-(2-methylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.21). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 using 66.20G and 69 to yield 69.21 (0.0405 g, 100% yield). MS ESI (neg.) m/e: 489.2 (M-H)⁺.

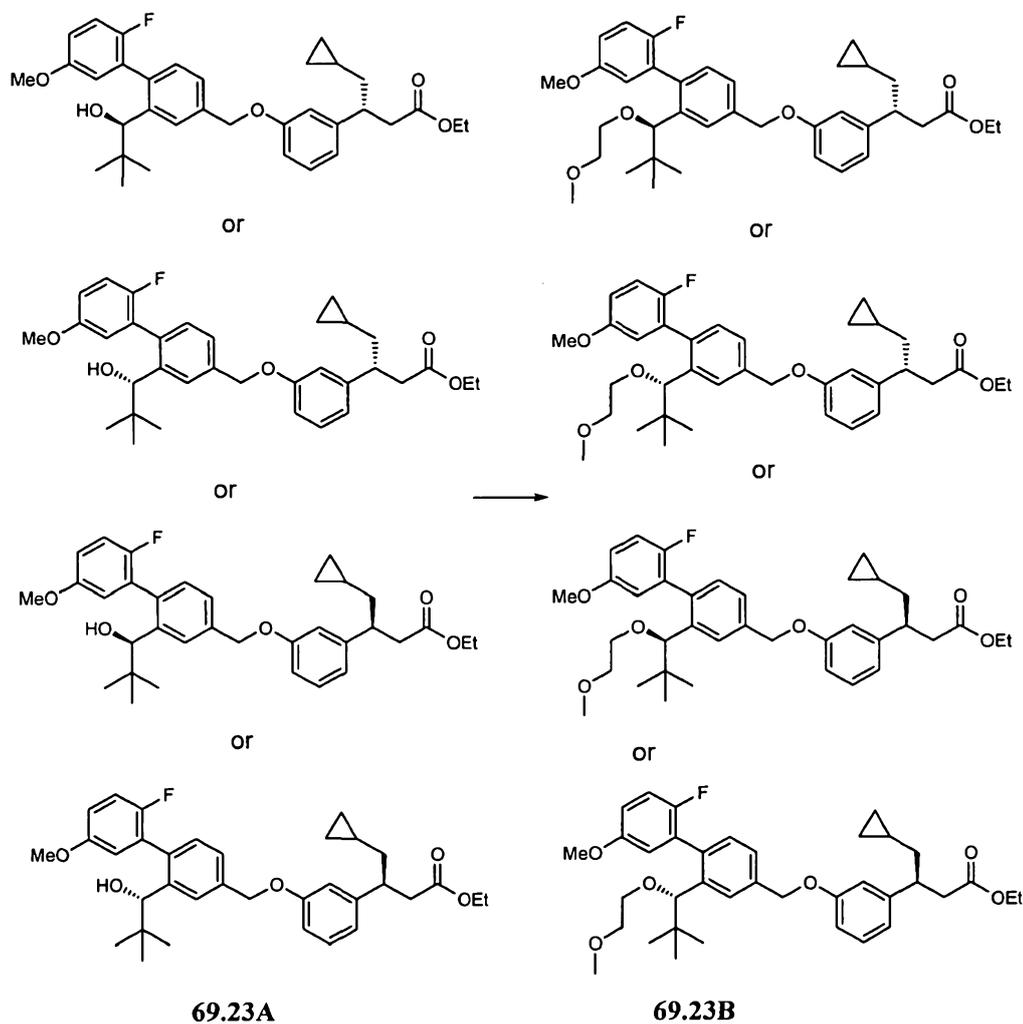
[01041] (3R)-4-Cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-((1R)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-((1S)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-((1R)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-((1S)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.22). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 using 69 and 66.18M or 66.18N (derived from peak two of the chiral separation of 66.18J on the OD-column, described herein) to yield 69.22 (0.0315 g, 75% yield over the two steps). MS ESI (neg.) m/e: 517.3 (M-H)⁺.

[01042] Example 69.23



[01043] Ethyl (3R)-4-cyclopropyl-3-(3-(((2'-fluoro-2-((1R)-1-hydroxy-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate or ethyl (3R)-4-cyclopropyl-3-(3-(((2'-fluoro-2-((1S)-1-hydroxy-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate or ethyl (3S)-4-cyclopropyl-3-(3-(((2'-fluoro-2-((1R)-1-hydroxy-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate or ethyl (3S)-4-cyclopropyl-3-(3-(((2'-fluoro-2-((1S)-1-hydroxy-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate (69.23A). To a stirred solution of 69 (0.500 g, 2.0 mmol) in THF (20.00 mL, 244 mmol) at 23°C was added 66.13H or 66.13I (0.64 g, 2.0 mmol, peak two from the chiral separation of 66.13G) followed by triphenylphosphine (0.79 g, 3.0 mmol), and then by dropwise addition of DEAD (0.48 mL, 3.0 mmol) over two hours. The reaction was then stirred for 21 hours. The reaction was then diluted with

water and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **69.23A** as a colorless oil (1.00 g, 91% yield).

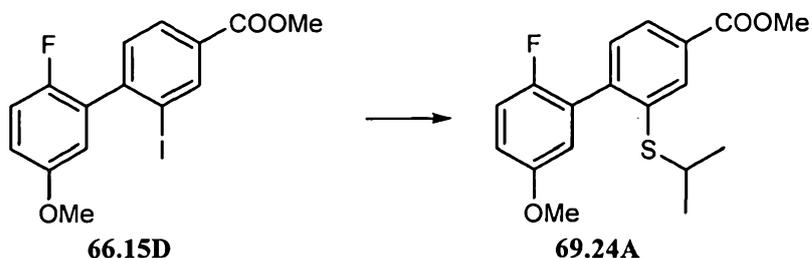


[01044] Ethyl (3R)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-((2-(methoxy)ethyl)oxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate or ethyl (3R)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-((2-(methoxy)ethyl)oxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate or ethyl (3S)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-((2-(methoxy)ethyl)oxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoate or ethyl (3S)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-((2-(methoxy)ethyl)oxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-

4-yl)methyl)oxy)phenyl)butanoate (69.23B). To a stirred solution of **69.23A** (0.050 g, 0.091 mmol) in DMF (2.00 mL) at 23°C was added 1-bromo-2-methoxyethane (0.019 g, 0.14 mmol)(commercially available from Aldrich) followed by sodium hydride (0.0026 g, 0.11 mmol). The reaction was stirred at 60°C for 21 hours, diluted with water and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-5% EtOAc in hexanes) to yield **69.23B** as a colorless oil (0.018 g, 33% yield)

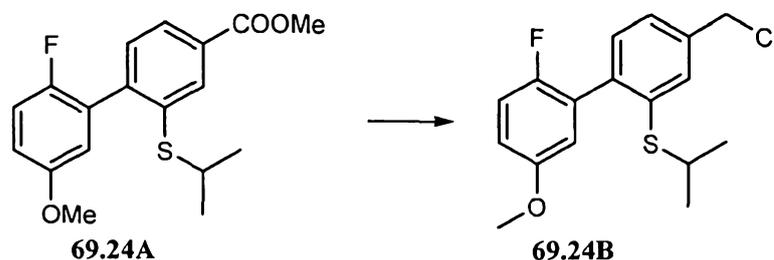
[01045] **(3R)-4-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-((2-(methoxy)ethyl)oxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-((2-(methoxy)ethyl)oxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-((2-(methoxy)ethyl)oxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-((2-(methoxy)ethyl)oxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.23).** The hydrolysis of **69.23B** was conducted in an analogous manner to Example 66.6 to yield **69.23** (0.0072 g, 42% yield). MS ESI (neg.) m/e: 577.3 (M-H)⁺.

[01046] **Example 69.24**

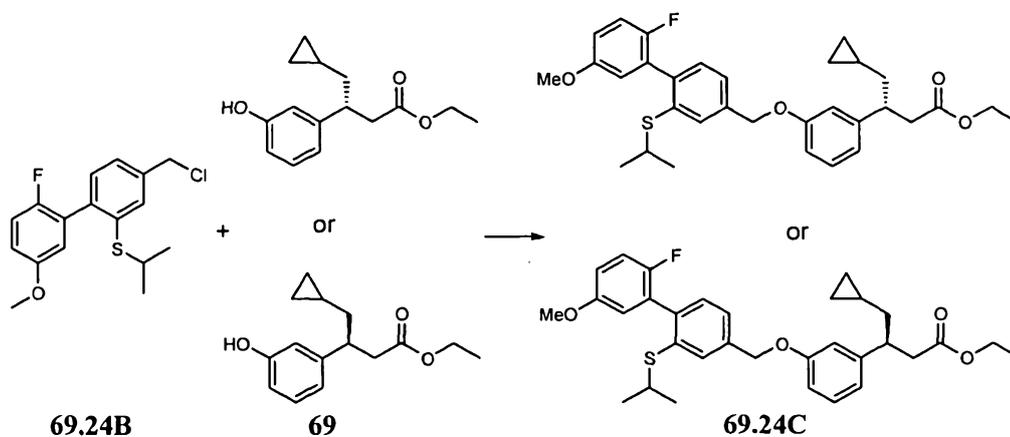


[01047] **2'-Fluoro-2-isopropylsulfanyl-5'-methoxy-biphenyl-4-carboxylic acid methyl ester (69.24A).** A tube was charged with **66.15D** (213 mg, 552 μmol), N-ethyl-N-isopropylpropan-2-amine (143 mg, 1103 μmol) and toluene, evacuated and back-filled with nitrogen three times. Pd₂(dba)₃, 4,5-bis(diphenylphosphino)-9,9-dimethyl-9H-xanthene (31.9 mg, 55.2 μmol) and propane-2-thiol (63.0 mg, 827 μmol) were added to the mixture and then the mixture was degassed three times. The suspension was refluxed overnight, filtered, and concentrated to give a residue which was purified by silica gel

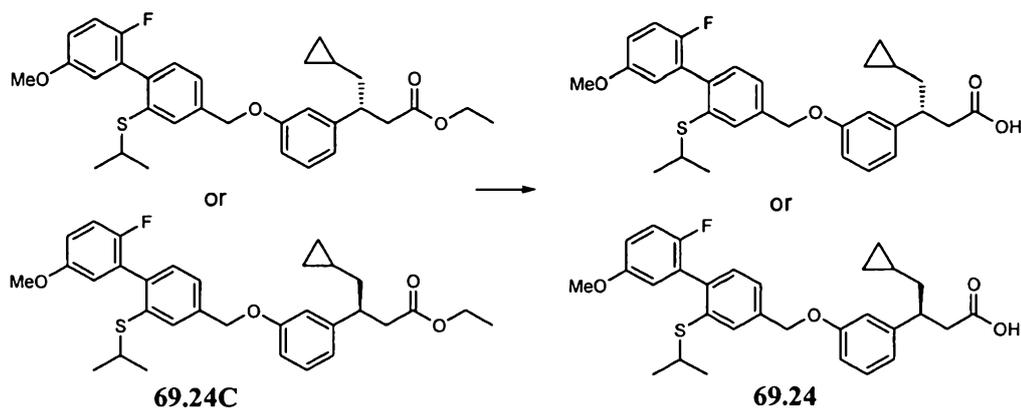
chromatography to give **69.24A** as a pale yellow solid (164mg, 89%). MS ESI m/e : 335.2 (M+1)⁺.



[01048] **4-Chloromethyl-2'-fluoro-2-isopropylsulfanyl-5'-methoxy-biphenyl (69.24B)**. The reduction and chlorination of **69.24A** was conducted in an analogous manner to that used to synthesize **8.10**. MS ESI m/e : 325.10 (M+H)⁺.



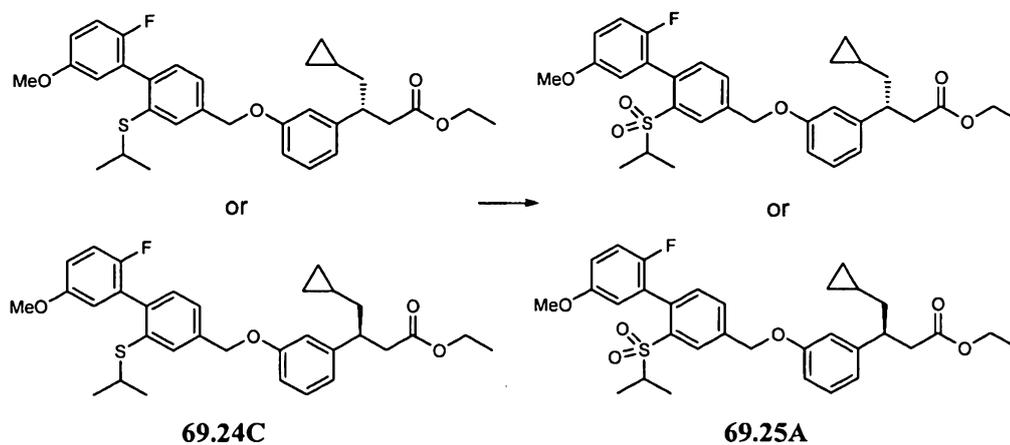
[01049] **(R)-4-Cyclopropyl-3-[3-(2'-fluoro-2-isopropylsulfanyl-5'-methoxy-biphenyl-4-ylmethoxy)-phenyl]-butyric acid ethyl ester or (S)-4-cyclopropyl-3-[3-(2'-fluoro-2-isopropylsulfanyl-5'-methoxy-biphenyl-4-ylmethoxy)-phenyl]-butyric acid ethyl ester (69.24C)** Compound **69.24C** was synthesized by a method analogous to the method used for preparation of compound **66.13P** from **69.24F** and **69**. MS ESI m/e : 537.3 (M+H)⁺.



[01050] (R)-4-Cyclopropyl-3-[3-(2'-fluoro-2-isopropylsulfanyl-5'-methoxy-biphenyl-4-ylmethoxy)-phenyl]-butyric acid or (S)-4-cyclopropyl-3-[3-(2'-fluoro-2-isopropylsulfanyl-5'-methoxy-biphenyl-4-ylmethoxy)-phenyl]-butyric acid (69.24).

Compound 69.24 was synthesized by a method analogous to the method used for compound 66.13 from 69.24C. MS ESI m/e : 526.2 (M+18). ^1H NMR (400 MHz, CDCl_3) δ ppm 7.52 (s, 1H), 7.29 (m, 1H), 7.24 (d, $J = 8\text{Hz}$, 1H), 7.20 (t, $J = 8\text{Hz}$, 1H), 7.01 (t, $J = 8\text{Hz}$, 1H) 6.83 (m, 4H), 6.76 (m, 1H), 5.06 (s, 2H), 3.77 (s, 3H), 3.20 (m, 2H), 2.72 (m, 1H), 2.65 (m, 1H), 1.67 (m, 1H), 1.32 (m, 1H), 1.15 (d, $J = 8\text{Hz}$, 6H), 0.49 (m, 1H), 0.34 (m, 2H), 0.04 (m, 2H).

[01051] Example 69.25

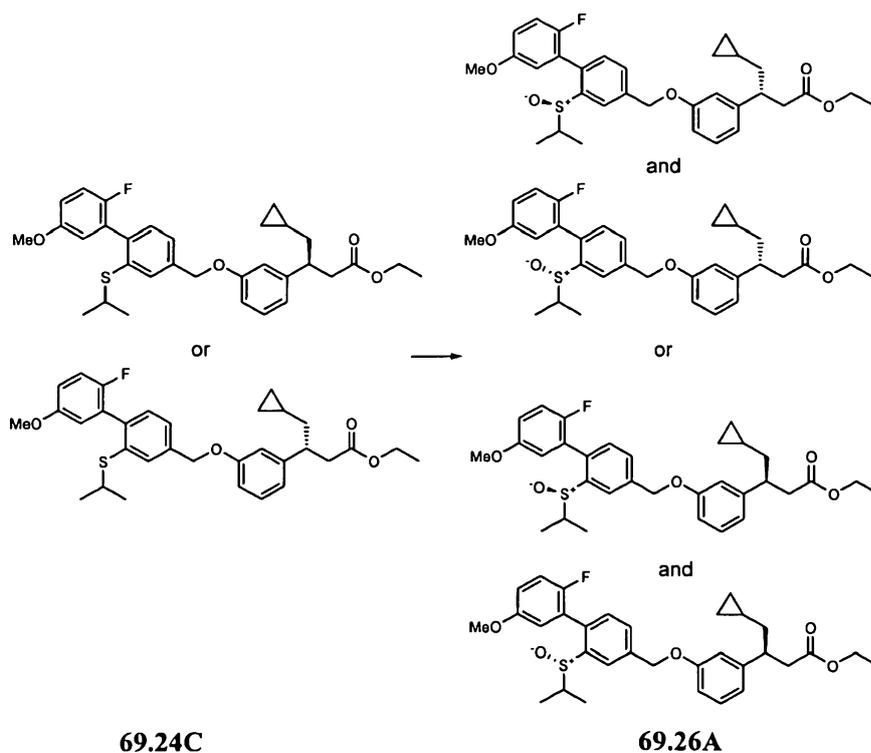


[01052] (R)-4-Cyclopropyl-3-[3-(2'-fluoro-5'-methoxy-2-(propane-2-sulfonyl)-biphenyl-4-ylmethoxy)-phenyl]-butyric acid ethyl ester or (S)-4-cyclopropyl-3-[3-(2'-fluoro-5'-methoxy-2-(propane-2-sulfonyl)-biphenyl-4-ylmethoxy)-phenyl]-butyric acid ethyl ester (69.25A). To a solution of 69.24C (70mg,

130 μmol) in DCM, was added 3-chloroperoxybenzoic acid (45 mg, 261 μmol) in one portion. The resulting mixture was stirred overnight and diluted with EtOAc. The organic phase was washed with saturated NaHCO_3 , water and brine, and dried over sodium sulfate. Solvent was removed in vacuo to give a residue which was purified by chromatography to give the product as an oil (60mg, 81%).

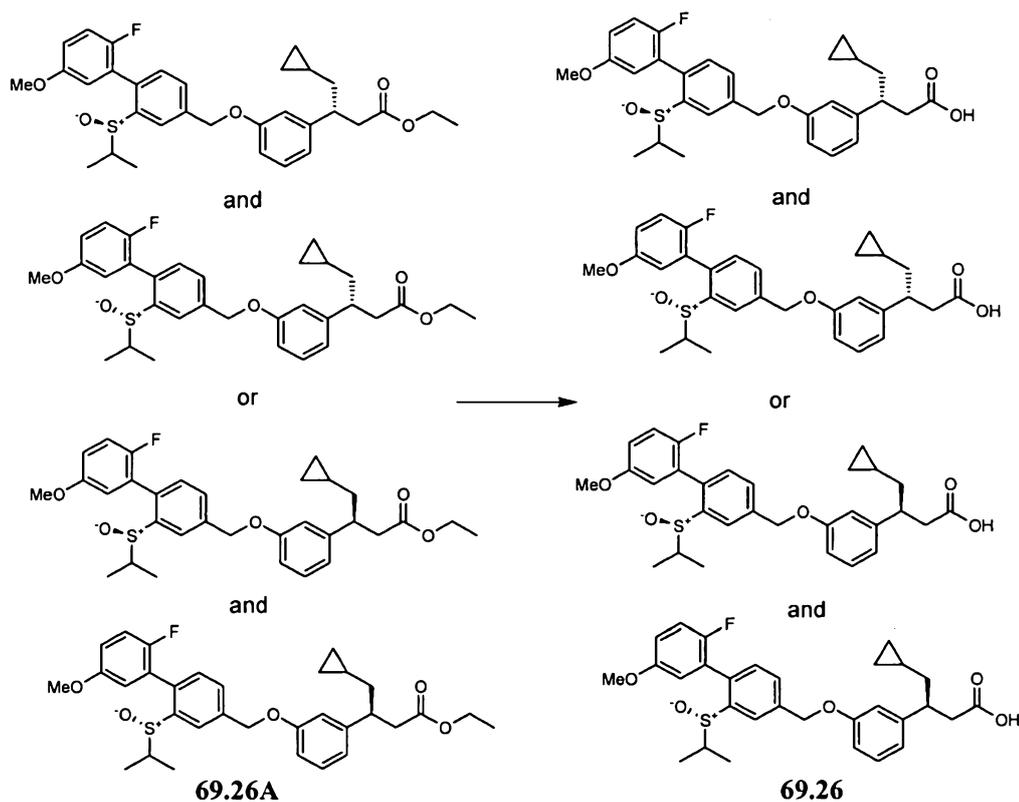
[01053] (R)-4-Cyclopropyl-3-{3-[2'-fluoro-5'-methoxy-2-(propane-2-sulfonyl)-biphenyl-4-ylmethoxy]-phenyl}-butyric acid or (S)-4-cyclopropyl-3-{3-[2'-fluoro-5'-methoxy-2-(propane-2-sulfonyl)-biphenyl-4-ylmethoxy]-phenyl}-butyric acid (**69.25**). Compound **69.25A** was hydrolyzed by a method analogous to the method used for compound **66.13** using **69.25A**. MS ESI m/e : 558.30 ($M+18$)⁺. ¹H NMR (400 MHz, CDCl_3) δ ppm 8.18 (s, 1H), 7.71 (d, $J = 8\text{Hz}$, 1H), 7.36 (d, $J = 8\text{Hz}$, 1H), 7.20 (t, $J = 8\text{Hz}$, 1H), 7.01 (m, 1H), 6.78-6.90 (m, 5H), 5.15 (s, 2H), 3.76 (s, 3H), 3.17 (m, 1H), 2.83 (m, 1H), 2.72 (m, 1H), 2.63 (m, 1H), 1.67 (m, 1H), 1.34 (m, 1H), 1.19 (d, $J = 8\text{Hz}$, 3H), 1.05 (d, $J = 8\text{Hz}$, 3H), 0.37 (m, 1H), 0.34 (m, 2H), 0.04 (m, 2H).

[01054] Example 69.26



[01055] (R)-4-Cyclopropyl-3-{3-[2'-fluoro-5'-methoxy-2-(propane-2-sulfonyl)-biphenyl-4-ylmethoxy]-phenyl}-butyric acid ethyl ester or (S)-4-Cyclopropyl-3-{3-

[2'-fluoro-5'-methoxy-2-(propane-2-sulfinyl)-biphenyl-4-ylmethoxy]-phenyl)-butyric acid ethyl ester (69.26A). To a solution of **69.24C** (63.6mg, 119 μ mol) in DCM (5 mL) at 0°C, was added 3-chloroperoxybenzoic acid (20.4 mg, 119 μ mol) in one portion. The mixture was stirred at room temperature overnight and then diluted with EtOAc. The organic layer was washed with saturated NaHCO₃, water and brine, and dried over sodium sulfate. After filtration, solvent was removed in vacuo to give a residue which was purified by chromatography to give an oil (48 mg, 73%).



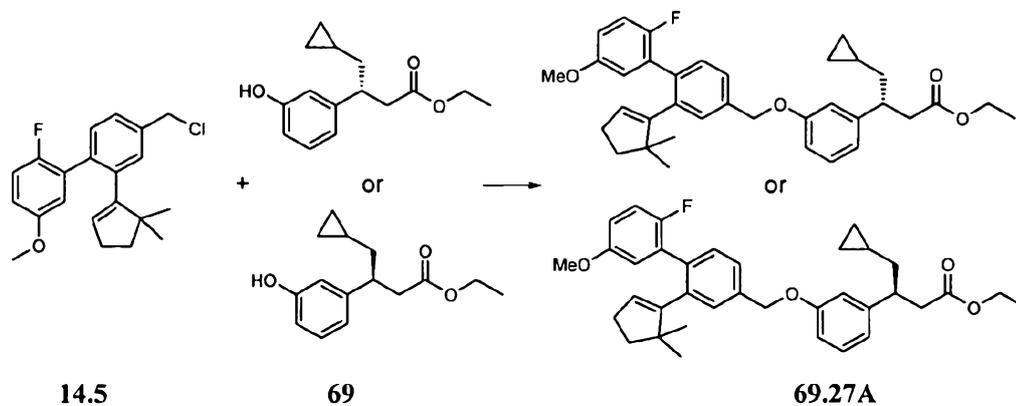
[01056] (R)-4-Cyclopropyl-3-{3-[2'-fluoro-5'-methoxy-2-(propane-2-sulfinyl)-biphenyl-4-ylmethoxy]-phenyl}-butyric acid or (S)-4-cyclopropyl-3-{3-[2'-fluoro-5'-methoxy-2-(propane-2-sulfinyl)-biphenyl-4-ylmethoxy]-phenyl}-butyric acid (69.26).

Compound **69.26** was prepared by a method analogous to the method used to synthesize compound **66.13** using **69.26A**. MS ESI m/e : 525.2 ($M+18$)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.94 (d, $J = 8$ Hz, 1H), 7.61 (m, 1H), 7.35 (t, $J = 8$ Hz, 1H), 7.18 (dt, $J = 8$ Hz, $J = 12$ Hz, 1H), 7.07 (dt, $J = 4$ Hz, $J = 8$ Hz, 1H), 6.88 (m, 5H), 5.26 (s, 2H), 3.78 (s, 1.5H), 3.79 (s, 1.5H), 3.17 (m, 1H), 2.74 (m, 1H), 2.57 (m, 2H), 1.75 (m,

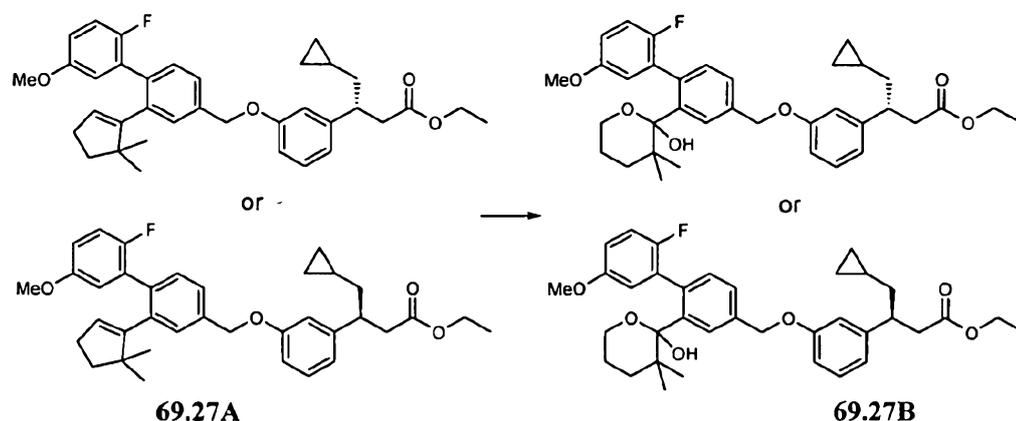
1H), 1.37 (m, 1H), 1.03 (d, J = 8Hz, 3H), 0.94 (dd, J = 4Hz, J = 8Hz, 3H), 0.56 (m, 1H), 0.38 (m, 2H), 0.04 (m, 2H).

[01057]

Example of 69.27

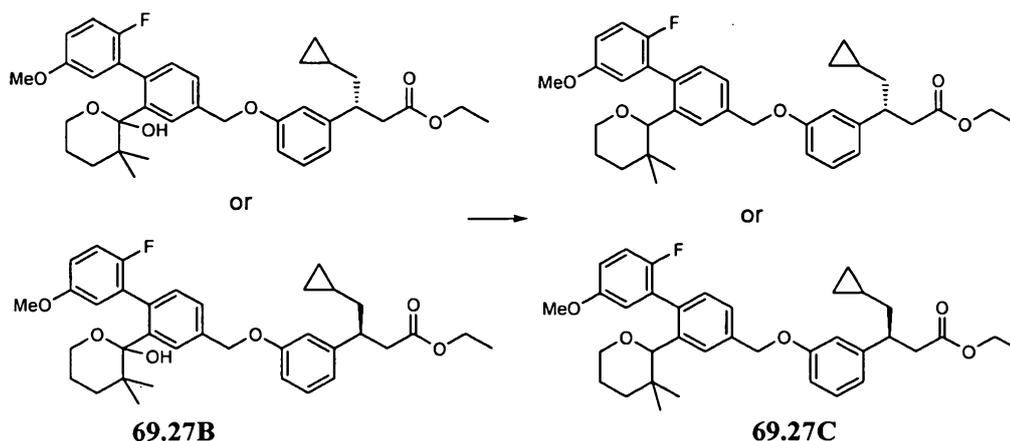


[01058] (R)-4-Cyclopropyl-3-{3-[2-(5,5-dimethyl-cyclopent-1-enyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-phenyl}-butyric acid ethyl ester or (S)-4-cyclopropyl-3-{3-[2-(5,5-dimethyl-cyclopent-1-enyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-phenyl}-butyric acid ethyl ester (69.27A). Compound 69.27A was synthesized by a method analogous to the method used in the synthesis of 66.13P using 14.5 and 69. MS ESI m/e: 557.3 (M+H)⁺.

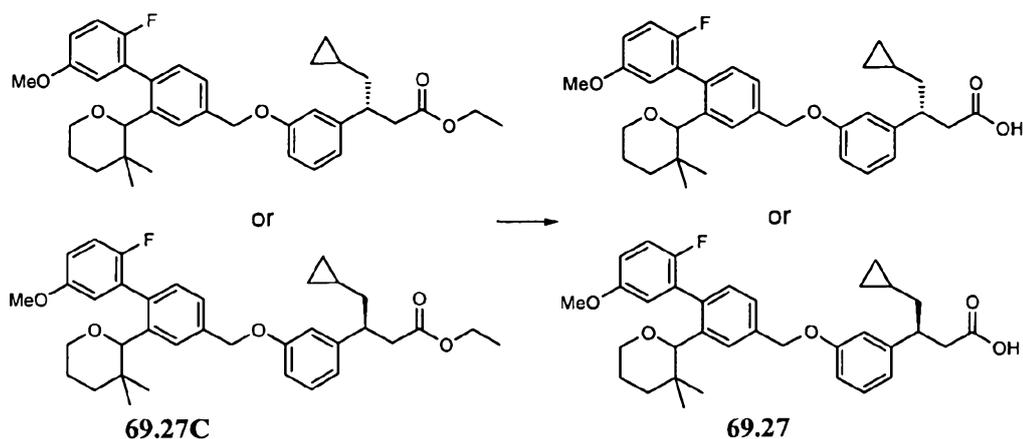


[01059] (R)-4-Cyclopropyl-3-{3-[2'-fluoro-2-(2-hydroxy-3,3-dimethyl-tetrahydro-pyran-2-yl)-5'-methoxy-biphenyl-4-ylmethoxy]-phenyl}-butyric acid ethyl ester or (S)-4-cyclopropyl-3-{3-[2'-fluoro-2-(2-hydroxy-3,3-dimethyl-tetrahydro-pyran-2-yl)-5'-methoxy-biphenyl-4-ylmethoxy]-phenyl}-butyric acid

ethyl ester (69.27B) To a solution of **69.27A** (40mg, 72 μmol) in a mixed solvent of DCM (0.5 mL) and MeOH (3 mL) at -78°C , was bubbled O_3 for 10 minutes. Nitrogen was then bubbled into the solution for 10 minutes. Sodium borohydride (8.2 mg, 216 μmol) was added, and the solution was warmed to room temperature overnight. Solvent was evaporated, the residue was diluted with EtOAc, the organic layer was washed with saturated NaHCO_3 , water, and brine. The organic layer was then dried, filtered, evaporated in vacuo to yield **69.27B** (36 mg) which was used without purification. MS ESI m/e : 608.3 ($\text{M}+18$)⁺.



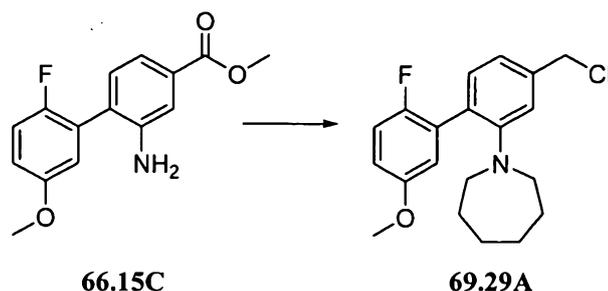
[01060] **(R)-4-Cyclopropyl-3-{3-[2-(3,3-dimethyl-tetrahydro-pyran-2-yl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-phenyl}-butyric acid ethyl ester or (S)-4-cyclopropyl-3-{3-[2-(3,3-dimethyl-tetrahydro-pyran-2-yl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-phenyl}-butyric acid ethyl ester (69.27C)**. To a solution of **66.27B** (30 mg, 51 μmol) in DCM (3 mL) at -78°C , was added 2,2,2-trifluoroacetic acid (TFA)(58 mg, 508 μmol). The mixture was stirred for 15 minutes and then triethylsilane (59 mg, 508 μmol) was added and the mixture was slowly returned to room temperature over 1 hour. The solvent was removed in vacuo to give a residue which was purified by silica gel chromatography to give an oil (20mg, 69%). MS ESI m/e : 575.3 ($\text{M}+\text{H}$)⁺.



[01061] (R)-4-Cyclopropyl-3-{3-[2-(3,3-dimethyl-tetrahydro-pyran-2-yl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-phenyl}-butyric acid or (S)-4-cyclopropyl-3-{3-[2-(3,3-dimethyl-tetrahydro-pyran-2-yl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-phenyl}-butyric acid (69.27). Compound 69.27 was synthesized from 69.27C by a method analogous to the method used to prepare compound 66.13 from 66.13P. MS ESI m/e : 564.3 ($M+18$)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.54 (m, 1H), 7.38 (m, 1H), 7.17 (m, 2H), 7.01 (m, 1H), 6.78 (m, 5H), 5.12 (m, 2H), 4.43 (m, 1/2H), 4.19 (s, 1/2H), 4.15 (m, 1H), 3.76 (m, 3H), 3.42 (m, 1H), 3.17 (m, 1H), 2.68 (m, 1H), 2.40-2.56 (m, 1H), 1.89 (m, 1H), 1.69 (m, 1H), 1.32 (m, 4H), 0.87 (m, 3H), 0.51 (m, 1H), 0.35 (m, 5H), 0.03 (m, 2H).

[01062] (3R)-4-Cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-(1-piperidinyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-(1-piperidinyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.28). Example 69.28 was prepared using an alkylation and hydrolysis which were conducted in an analogous manner to Example 66.6 (using 67.20E and 69, described herein) to yield 67.28 (37.7 mg, 88% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.25 (2 H, m), 7.12 (4 H, m), 6.87 (4 H, m), 5.02 (2 H, s), 3.78 (3 H, s), 3.24 (1 H, m), 2.78 (4 H, m), 2.76 (1 H, m), 2.66 (1 H, m), 1.69 (1 H, m), 1.40 (6 H, m), 1.32 (1 H, ddd, $J=13.9, 7.8, 6.1$ Hz), 0.54 (1 H, m), 0.39 (2 H, m), 0.08 (2 H, m). MS ESI (pos.) m/e : 518.0 ($M+H$)⁺.

[01063] Example of 69.29



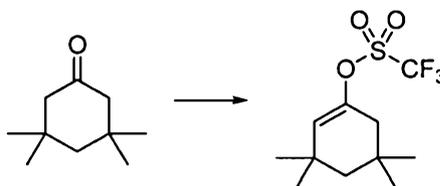
[01064] **1-(4-(Chloromethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)azepane (69.29A)**. An acylation, reduction and chlorination strategy was employed similar to that of Example 67.20E (described herein) to yield 67.29A. 6-Commercially available bromohexanoyl chloride (0.9 mL, 6.02 mmol) was used as the acylating reagent.. MS ESI (pos.) m/e: 348.0 (M+H)⁺.

[01065] **(3R)-3-(3-(((2-(1-Azepanyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-cyclopropylbutanoic acid or (3S)-3-(3-(((2-(1-azepanyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-cyclopropylbutanoic acid (69.29)**. The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 using 67.29A and 69 to yield 69.29. The residue was purified with HPLC using 30-90% solvent B (0.1% TFA in acetonitrile) over 45 minutes to afford 69.29 as a TFA salt (4.0 mg). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.70 (1 H, s), 7.51 (1 H, d, J=7.8 Hz), 7.31 (1 H, d, J=7.8 Hz), 7.22 (1 H, t, J=7.8 Hz), 7.11 (1 H, t, J=9.0 Hz), 6.97 (1 H, ddd, J=8.9, 3.9, 3.6 Hz), 6.89 (3 H, m), 6.78 (1 H, s), 5.22 (2 H, s), 3.82 (3 H, m), 3.60 (4 H, dd, J=6.5, 3.7 Hz), 3.22 (1 H, m), 2.77 (1 H, dd, J=15.5, 5.3 Hz), 2.54 (1 H, dd, J=15.3, 9.8 Hz), 1.83 (4 H, s), 1.71 (1 H, ddd, J=13.9, 8.0, 5.9 Hz), 1.61 (4 H, s), 1.34 (1 H, dt, J=14.2, 7.2 Hz), 0.59 (1 H, m), 0.44 (2 H, m), 0.05 (1 H, td, J=8.9, 4.9 Hz), -0.02 (1 H, td, J=8.9, 4.9 Hz). MS ESI (pos.) m/e: 532.0 (M+H)⁺.

[01066] **(3R)-4-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.30)**. The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 66.43I and 69, described herein) to yield 69.30 (38.9 mg, 78% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.36 (1 H, d, J=7.4 Hz), 7.24 (1 H, t, J=7.8 Hz), 7.08 (1 H, d, J=9.8 Hz), 6.98 (1 H, t, J=9.0 Hz), 6.90 (3 H, m), 6.84 (2 H, m), 5.51 (1 H, s), 5.17 (2 H, s),

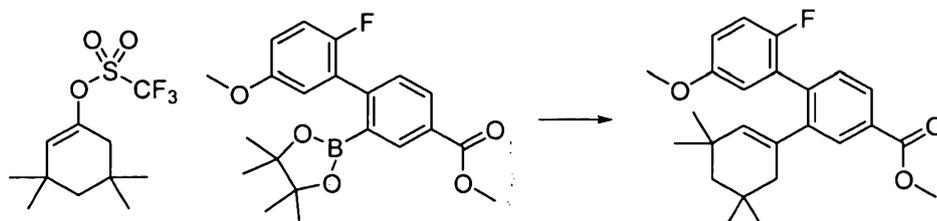
3.76 (3 H, s), 3.27 (1 H, m), 2.79 (1 H, m), 2.69 (1 H, m), 2.24 (2 H, td, $J=7.0, 2.3$ Hz), 1.72 (1 H, ddd, $J=13.9, 8.4, 5.9$ Hz), 1.65 (2 H, t, $J=6.8$ Hz), 1.35 (1 H, ddd, $J=13.9, 7.8, 6.1$ Hz), 0.81 (6 H, s), 0.57 (1 H, m), 0.42 (2 H, m), 0.07 (1 H, m), -0.01 (1 H, m). MS ESI (neg.) m/e : 544.9 (M-H)⁻.

[01067] **Example 69.31**



69.31A

[01068] **3,3,5,5-Tetramethylcyclohex-1-enyl trifluoromethanesulfonate (69.31A)**. Compound **69.31A** was prepared from 3,3,5,5-tetramethylcyclohexanone (available from Aldrich) according to the analogous method described for the synthesis of A.2.

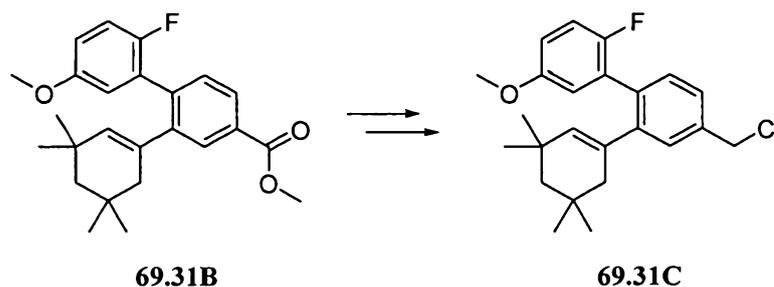


69.31A

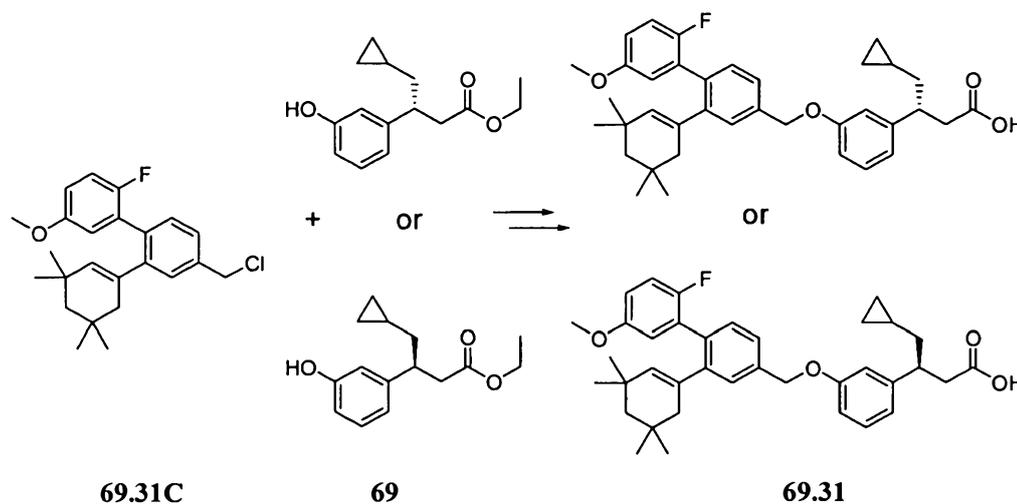
66.56A

69.31B

[01069] **Methyl 2'-fluoro-5'-(methoxy)-2-(3,3,5,5-tetramethyl-1-cyclohexen-1-yl)-1,1'-biphenyl-4-carboxylate (69.31B)**. A screw-cap vial was charged with **66.31A** (0.556 g, 1.94 mmol), THF (10 mL), **66.56A** (0.500 g, 1.29 mmol), potassium phosphate (0.824 g, 3.88 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (commercially available from Aldrich) (0.165 g, 0.401 mmol), palladium(II) acetate (0.0291 g, 0.129 mmol), and water (0.117 mL, 6.47 mmol). The mixture was purged with argon and stirred for 48 hours at room temperature under an argon balloon. Additional 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (0.165 g, 0.401 mmol), palladium(II) acetate (0.0291 g, 0.129 mmol), and **69.31A** (0.556 g, 1.94 mmol) were added, and stirring was continued for 16 hours at room temperature under argon. The mixture was filtered through silica gel (EtOAc) and concentrated. The crude product was purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **69.31B** (0.300 g, 58% yield) as a colorless oil.



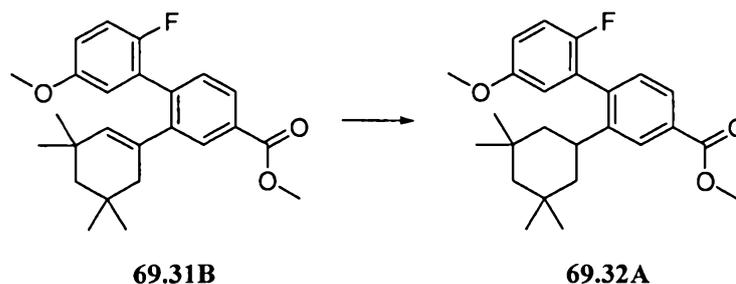
[01070] **4-(Chloromethyl)-2'-fluoro-5'-(methoxy)-2-(3,3,5,5-tetramethyl-1-cyclohexen-1-yl)-1,1'-biphenyl (69.31C)**. Compound **69.31C** was prepared from **69.31B** according to the analogous procedures described in Example 66.56.



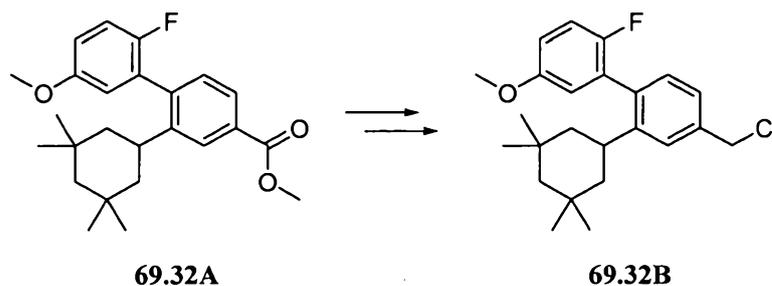
[01071] **(3R)-4-Cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-(3,3,5,5-tetramethyl-1-cyclohexen-1-yl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid** or **(3S)-4-cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-(3,3,5,5-tetramethyl-1-cyclohexen-1-yl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.31)**.

Example **69.31** was prepared from **69** and **69.31C** according to the analogous methods described in Example 7. MS ESI (pos.) m/e: 588.3 (M+H₂O)⁺, 593.3 (M+Na)⁺.

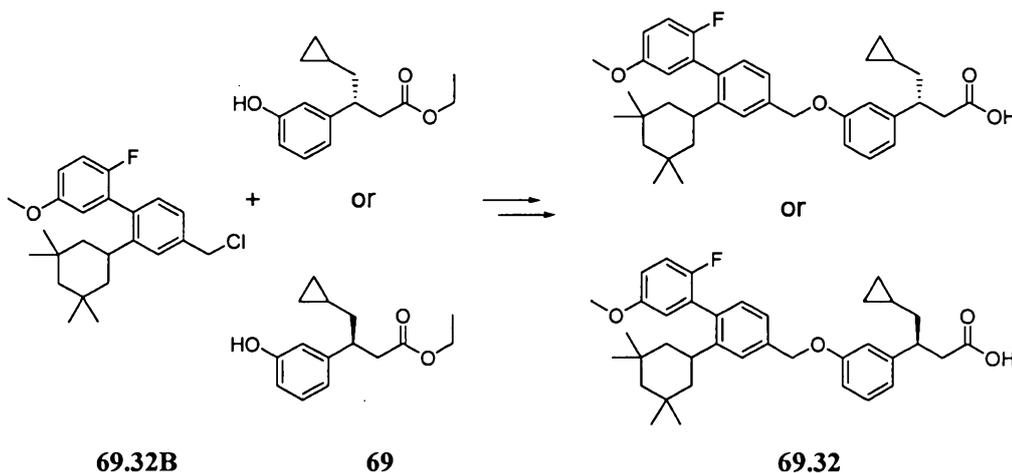
[01072] **Example 69.32**



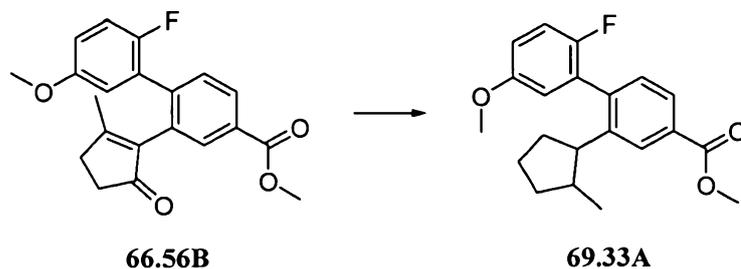
[01073] **Methyl 2'-fluoro-5'-(methoxy)-2-(3,3,5,5-tetramethylcyclohexyl)-1,1'-biphenyl-4-carboxylate (69.32A)**. A screw-cap pressure tube was charged with **69.31B** (0.22 g, 0.55 mmol), 1:1 EtOAc/MeOH (10 mL), and platinum(IV) oxide (0.025 g, 0.11 mmol). The tube was purged three times with H₂ at 50 psi and sealed, and the contents were stirred overnight. The mixture was diluted with EtOAc, filtered through silica gel (EtOAc), and concentrated. The crude product was purified by silica gel flash chromatography (0-8% EtOAc/hexane) to afford **69.32A** (0.13 g, 59% yield) as a colorless oil.



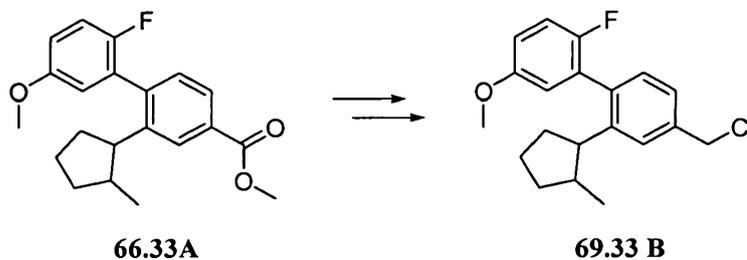
[01074] **4-(Chloromethyl)-2'-fluoro-5'-(methoxy)-2-(3,3,5,5-tetramethylcyclohexyl)-1,1'-biphenyl (69.32B)**. Compound **69.32B** was prepared from **69.32A** according to the analogous methods described in Example 66.56.



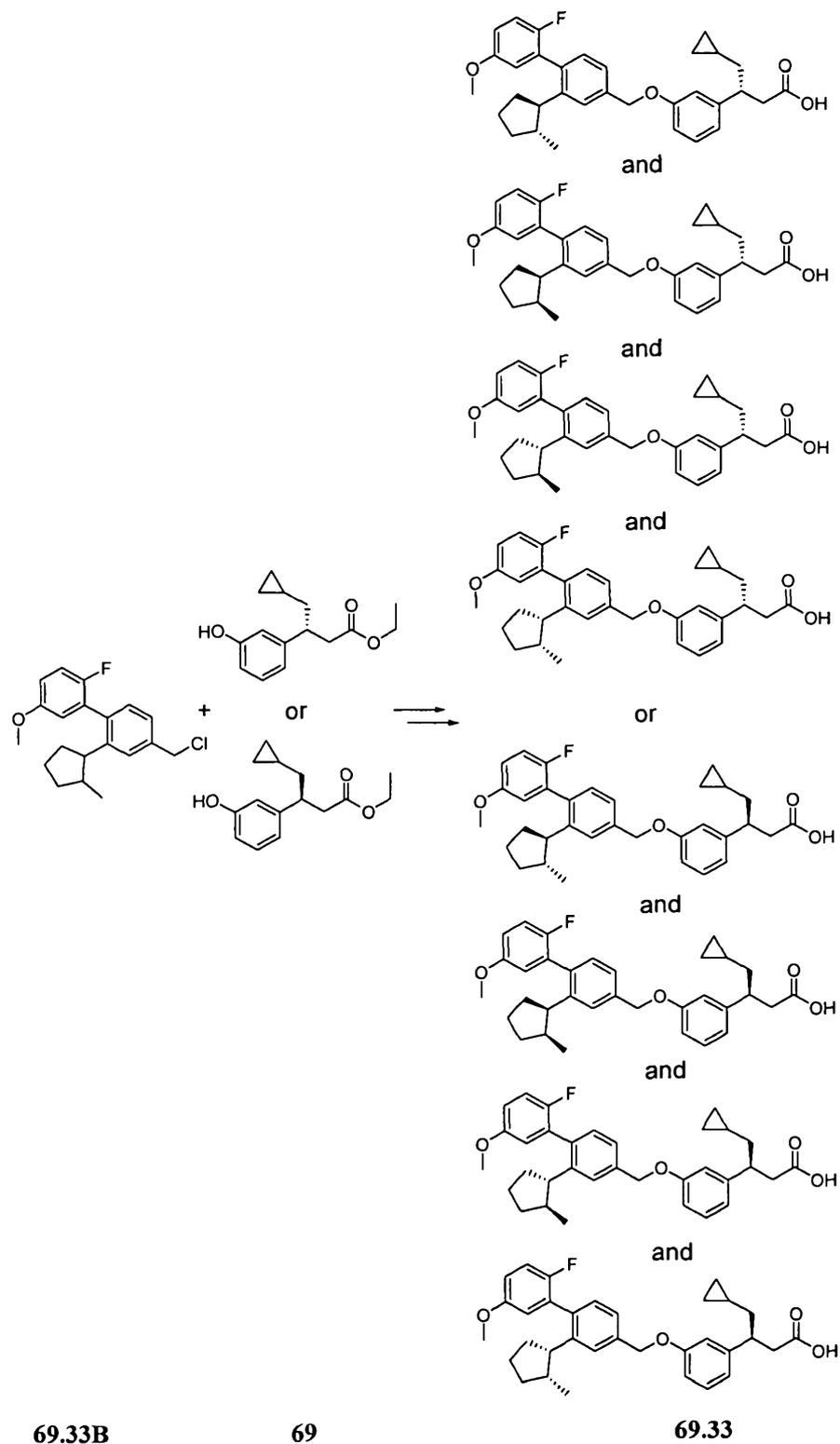
[01075] **(3R)-4-Cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-(3,3,5,5-tetramethylcyclohexyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-(3,3,5,5-tetramethylcyclohexyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.32)**. **69.32** was prepared from **69** and **69.32B** according to the analogous methods described in Example 7. MS ESI (pos.) m/e: 573.3 (M+H)⁺, 590.3 (M+H₂O)⁺, 595.3 (M+Na)⁺.

[01076] Example 69.33

[01077] Methyl 2'-fluoro-2-(2-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (69.33A). A screw-cap pressure tube was charged with **66.56B** (0.31 g, 0.87 mmol), MeOH (10 mL), and platinum(IV) oxide (0.040 g, 0.17 mmol). The tube was purged three times with H₂ at 45 psi and sealed, and the contents were stirred overnight. The mixture was diluted with EtOAc, filtered through silica gel (EtOAc), and concentrated. The crude product was purified by silica gel flash chromatography (0-20% EtOAc/hexane) to afford **69.33A** (1:1 d.r.) (0.040 g) as a colorless oil.



[01078] 4-(Chloromethyl)-2'-fluoro-2-(2-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl (69.33B). **69.33B** (1:1 d.r.) was prepared from **66.33A** (1:1 d.r.) according to the analogous methods described in Example 66.56.



[01079] **69.33B** **69** **69.33**
(3R)-4-Cyclopropyl-3-(3-(((2'-fluoro-2-(2-methylcyclopentyl)-5'

(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2'-fluoro-2-(2-methylcyclopentyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.33). Example 69.33 (1:1:1:1 d.r.) was prepared from 69 and 69.33B (1:1 d.r.) according to the analogous methods described in Example 7. MS ESI (pos.) m/e: 534.2 (M+H₂O)⁺, 539.2 (M+Na)⁺.

[01080] (3R)-4-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.34). MS ESI (neg.) m/e: 547.3 (M-H)⁺.

[01081] (3R)-4-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (3R)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.35). MS ESI (neg.) m/e: 533.2 (M-H)⁺.

[01082] (3R)-4-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.36). MS ESI (neg.) m/e: 543.2 (M-H)⁺.

[01083] (3R)-4-Cyclopropyl-3-(3-(((2-((ethoxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((ethoxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.37). The alkylation and hydrolysis were

conducted in an analogous manner to Example 67.23 using 67.23C and 69 to yield 67.37. MS ESI (neg.) m/e: 491 (M-H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.60 (m, 1H), 7.44-7.46 (m, 1H), 7.18-7.27 (m, 3H), 6.96-7.00 (m, 1H), 6.91 (m, 1H), 6.82-6.87 (m, 3H), 5.15 (s, 2H), 4.29 (s, 2H), 3.76 (s, 3H), 3.36 (m, 2H), 3.07 (m, 1H), 2.65 (m, 1H), 2.48 (m, 1H), 1.55 (m, 2H), 1.33 (m, 1H), 1.04 (t, 3H), 0.45 (m, 1H), 0.27 (m, 2H), 0.02 (m, 1H), -0.09 (m, 1H).

[01084] (3R)-4-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)-3-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)-3-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)-3-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)-3-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.38). The alkylation and hydrolysis were conducted in an analogous manner to Example 67.24 using peak one from the chiral separation of 67.24A on the OD column and 69 to yield 69.38. MS ESI (neg.) m/e: 545 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.53 (m, 1H), 7.42-7.45 (m, 1H), 7.16-7.24 (m, 2H), 7.01-7.07 (m, 1H), 6.82-6.90 (m, 4H), 6.73-6.75 (m, 1H), 5.70-5.77 (m, 1H), 5.14 (m, 1H), 4.70-4.85 (m, 2H), 4.22 (m, 1H), 3.81 (m, 3H), 3.32 (m, 3H), 2.62-2.79 (m, 3H), 1.70-1.73 (m, 2H), 1.29 (m, 6H), 1.18 (m, 2H), 0.90-0.99 (m, 2H), 0.53 (m, 1H), 0.37 (m, 1H), 0.00-0.10 (m, 2H).

[01085] (3R)-4-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)-3-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)-3-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)-3-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)-3-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.39). The alkylation and hydrolysis were conducted in an analogous manner to Example 67.24 (using peak two from the chiral separation of 67.24A on the OD column and 69) to yield 69.39. This is a diastereomer of 69.38. MS ESI (neg.) m/e: 545 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.53 (m, 1H), 7.42-7.45 (m, 1H), 7.16-7.24 (m, 2H), 7.01-7.07 (m,

1H), 6.82-6.90 (m, 4H), 6.73-6.75 (m, 1H), 5.70-5.77 (m, 1H), 5.14 (m, 1H), 4.70-4.85 (m, 2H), 4.22 (m, 1H), 3.81 (m, 3H), 3.32 (m, 3H), 2.62-2.79 (m, 3H), 1.70-1.73 (m, 2H), 1.26 (m, 6H), 1.18 (m, 2H), 0.76-0.90 (m, 2H), 0.53 (m, 1H), 0.37 (m, 1H), 0.00-0.10 (m, 2H).

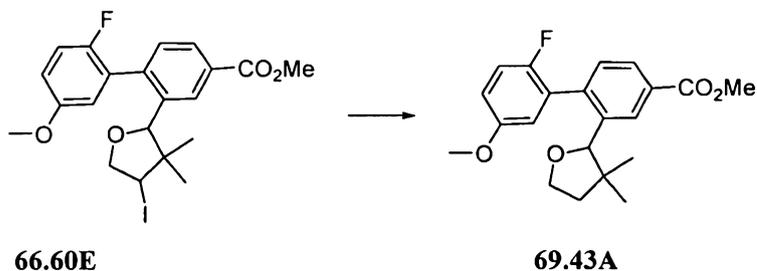
[01086] (3R)-4-Cyclopropyl-3-(3-(((2'-fluoro-2-((1S)-1-hydroxy-2,2-dimethyl-3-butenyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((2'-fluoro-2-((1R)-1-hydroxy-2,2-dimethyl-3-butenyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2'-fluoro-2-((1S)-1-hydroxy-2,2-dimethyl-3-butenyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2'-fluoro-2-((1R)-1-hydroxy-2,2-dimethyl-3-butenyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.40). The alkylation and hydrolysis were conducted in an analogous manner to Example 67.25 (using 67.25A (derived from peak one from the chiral separation of 67.24A) on the OD column and 69) to yield 69.40. MS ESI (neg.) m/e: 531 (M-H). ¹H NMR (400 MHz, CD₃OD) δ ppm 7.66-7.71 (d, 1H), 7.20 (m, 1H), 7.05-7.18 (m, 3H), 6.82-6.95 (m, 5H), 5.78 (m, 1H), 5.14 (m, 2H), 4.71 (m, 2H), 3.79 (s, 3H), 3.13 (m, 1H), 2.52-2.58 (m, 2H), 1.65 (m, 2H), 1.34 (m, 1H), 1.19 (m, 1H), 0.81 (s, 3H), 0.71 (s, 3H), 0.48 (m, 1H), 0.34 (m, 2H), 0.01 (m, 1H), -0.07 (m, 1H).

[01087] (3R)-4-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.41). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.62 (using 66.62E (derived from peak two from the chiral separation of 66.62B) on the OD column and 69) to yield 69.41. MS ESI (neg.) m/e: 547 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.58 (m, 1H), 7.42 (m, 1H), 7.20-7.23 (m, 2H), 7.05 (m, 1H), 6.84-6.90 (m, 4H), 6.75 (m, 1H), 5.15 (s, 2H), 4.06-4.29 (m, 1H), 3.80 (s, 3H), 3.23-3.29 (m, 3H), 2.73-2.80 (m, 1H), 2.61-2.67 (m, 2H), 1.72 (m, 1H), 1.35 (m, 2H), 1.07 (m, 1H), 0.80 (m, 1H), 0.72 (s, 3H), 0.61 (m, 3H), 0.49-0.52 (m, 4H), 0.36 (m, 2H), 0.02-0.04 (m, 2H).

[01088] (3R)-4-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.41).

(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.42). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.62 (using 66.62E (derived from peak one from the chiral separation of 66.62B) on the OD column and 69) to yield 69.42. MS ESI (neg.) m/e: 547 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.58 (m, 1H), 7.4-7.44 (m, 1H), 7.20-7.23 (m, 2H), 7.18 (m, 1H), 6.83-6.90 (m, 4H), 6.74 (m, 1H), 5.15 (m, 2H), 4.05-4.29 (m, 1H), 3.80 (s, 3H), 3.23-3.28 (m, 3H), 2.64-2.78 (m, 2H), 1.72 (m, 1H), 1.35 (m, 2H), 1.07 (m, 1H), 0.80 (m, 1H), 0.71 (s, 3H), 0.60 (m, 3H), 0.48 (m, 3H), 0.36-0.39 (m, 2H), 0.02-0.04 (m, 2H).

[01089] **Example 69.43**



[01090] **Methyl 2-(3,3-dimethyltetrahydro-2-furanyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (69.43A)**. To a solution of 66.60E (0.388 g, 0.801 mmol) in MeOH (17 mL)(degassed by N₂), was added palladium-carbon (0.0853 g, 0.801 mmol). The resulting mixture was stirred at room temperature under H₂ for 23 hours. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:19 EtOAc / hexane) and gave 65mg of 69.43A. MS ESI (pos.) m/e: 376 (M+18)⁺.

[01092] (2S)-2-(4-(Bromomethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-3,3-dimethyltetrahydrofuran or (2R)-2-(4-(bromomethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-3,3-dimethyltetrahydrofuran (69.43D). The bromination was conducted in an analogous manner to Example 66.62 to yield 69.43D.

[01093] (3R)-4-Cyclopropyl-3-(3-(((2-((2S)-3,3-dimethyltetrahydro-2-furanyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((2-((2R)-3,3-dimethyltetrahydro-2-furanyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((2S)-3,3-dimethyltetrahydro-2-furanyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((2R)-3,3-dimethyltetrahydro-2-furanyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.43). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.62 (using 69.43D (derived from peak two from the chiral separation of the reduction product of 66.43A) on the OD column and 69) to yield 69.43. MS ESI (neg.) m/e: 531 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.56 (m, 1H), 7.40 (m, 1H), 7.17 (m, 2H), 7.03 (m, 1H), 6.81-6.83 (m, 5H), 5.20 (m, 2H), 4.71-4.83 (m, 1H), 3.94-4.20 (m, 2H), 3.78 (m, 3H), 3.21 (m, 2H), 2.70 (m, 1H), 2.37 (m, 1H), 1.77 (m, 2H), 1.29 (m, 2H), 0.89 (s, 1H), 0.68 (m, 6H), 0.39-0.41 (m, 2H), 0.08 (m, 2H).

[01094] (3R)-4-cyclopropyl-3-(3-(((2-((2S)-3,3-dimethyltetrahydro-2-furanyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((2-((2R)-3,3-dimethyltetrahydro-2-furanyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((2S)-3,3-dimethyltetrahydro-2-furanyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((2R)-3,3-dimethyltetrahydro-2-furanyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.44). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.62 (using 69.43D (derived from peak one from the chiral separation of the reduction product of 66.43A) on the OD column and 69, described herein) to yield 69.44. MS ESI (neg.) m/e: 531 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.56 (m, 1H), 7.40 (m, 1H), 7.17 (m, 2H), 7.03 (m, 1H), 6.81-6.83 (m, 5H), 5.18 (m, 2H), 4.71-4.83 (m, 1H), 3.94-4.20 (m, 2H), 3.79 (m, 3H), 3.15 (m, 1H), 2.50-2.70 (m, 2H), 1.77 (m,

2H), 1.29 (m, 2H), 0.89 (m, 1H), 0.68 (m, 6H), 0.51 (m, 1H), 0.40 (m, 2H), 0-0.08 (m, 2H).

[01095] **(3R)-4-Cyclopropyl-3-(3-(((2'-fluoro-2-(((3-methyl-2-butenyl)oxy)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2'-fluoro-2-(((3-methyl-2-butenyl)oxy)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.45).** The alkylation and hydrolysis were conducted in an analogous manner to Example 66.62 (using 67.27C and 69, described herein) to yield 69.45. MS ESI (neg.) m/e: 531 (M-H). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.60 (m, 1H), 7.42 (m, 1H), 7.21-7.29 (m, 2H), 7.02-7.07 (m, 1H), 6.82-6.89 (m, 5H), 5.24 (m, 1H), 5.15 (s, 2H), 4.37 (s, 2H), 3.92 (d, 2H), 3.80 (s, 3H), 3.18 (m, 1H), 2.54-2.76 (m, 2H), 1.75 (m, 1H), 1.70 (s, 3H), 1.58 (s, 3H), 1.35 (m, 1H), 0.56 (m, 1H), 0.37 (m, 2H), 0.00 (m, 2H).

[01096] **(3R)-4-Cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-(1-pyrrolidinylmethyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2'-fluoro-5'-(methoxy)-2-(1-pyrrolidinylmethyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.46).** The alkylation and hydrolysis were conducted in an analogous manner to Example 66.65 using 66.65C and 69 to yield 69.46. MS ESI (neg.) m/e: 516 (M-H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.68 (m, 1H), 7.84 (m, 1H), 7.62 (m, 1H), 7.39 (d, 1H), 7.21-7.31 (m, 2H), 7.04-7.07 (m, 1H), 6.86-6.96 (m, 4H), 5.18 (s, 2H), 4.04-4.40 (m, 2H), 3.79 (s, 3H), 3.30 (m, 4H), 3.08 (m, 1H), 2.59-2.70 (m, 2H), 2.64 (m, 1H), 1.80 (m, 4H), 1.57 (m, 1H), 1.34 (m, 1H), 0.45 (m, 1H), 0.28 (m, 2H), 0.02 (m, 1H), -0.80 (m, 1H).

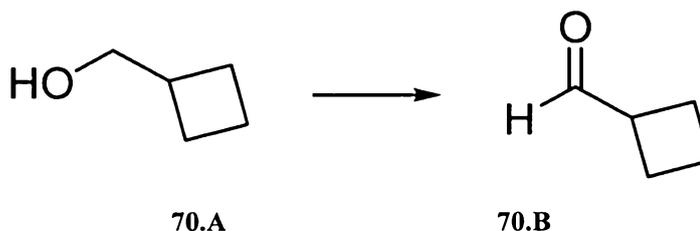
[01097] **(3R)-4-Cyclopropyl-3-(3-(((2-(((2R,5R)-2,5-dimethyl-1-pyrrolidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-(((2R,5R)-2,5-dimethyl-1-pyrrolidinyl)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (69.47).** The alkylation and hydrolysis were conducted in an analogous manner to Example 66.62 (using 66.71C and 69, described herein) to yield 69.47. After removing solvent, 66.69 (TFA salt), 15mg, was obtained. MS ESI (neg.) m/e: 544 (M-H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.55 (M, 1H), 7.87 (m, 1H), 7.61-7.63 (m, 1H), 7.41 (m, 1H), 7.31 (m, 1H), 7.22 (m, 1H), 7.08 (m, 1H), 6.85-6.91 (m, 4H), 5.19 (s, 2H), 4.10-4.40 (m, 1H), 3.78 (s, 3H), 3.08 (m, 1H), 2.64 (m, 1H), 2.08 (m, 1H), 1.56 (m, 3H), 1.35 (m, 3H), 1.00-1.10 (m, 3H), 0.85 (m, 1H), 0.48

(m, 1H), 0.28 (m, 2H), -0.09-0.00 (m, 2H)

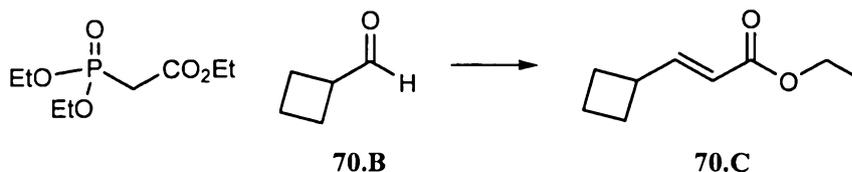
[01098] **(3R)-3-(3-(((2-(1-Azepanylmethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-cyclopropylbutanoic acid or (3S)-3-(3-(((2-(1-azepanylmethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-cyclopropylbutanoic acid (69.48)**. The alkylation and hydrolysis were conducted in an analogous manner to Example 66.62 (using 66.73C and 69, described herein) to yield 69.48. After removing solvent, 69.48 (TFA salt), 26 mg, was obtained. MS ESI (neg.) m/e: 544 (M-H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.40 (m, 1H), 7.91 (m, 1H), 7.63-7.65 (m, 1H), 7.41 (m, 1H), 7.22-7.33 (m, 1H), 7.06-7.10 (m, 1H), 6.86-6.97 (m, 4H), 5.18 (s, 2H), 4.05-4.20 (m, 1H), 3.79 (s, 3H), 3.09 (m, 2H), 2.90-3.00 (m, 2H), 2.65 (m, 1H), 1.50-1.62 (m, 8H), 1.36 (m, 1H), 0.44 (m, 1H), 0.29 (m, 2H), 0.01 (m, 1H), -0.08 (m, 1H).

[01099] **Example 70**

[01100] **Synthesis of methyl (3S)-3-cyclobutyl-3-(3-hydroxyphenyl)propanoate and methyl (3R)-3-cyclobutyl-3-(3-hydroxyphenyl)propanoate (70).**

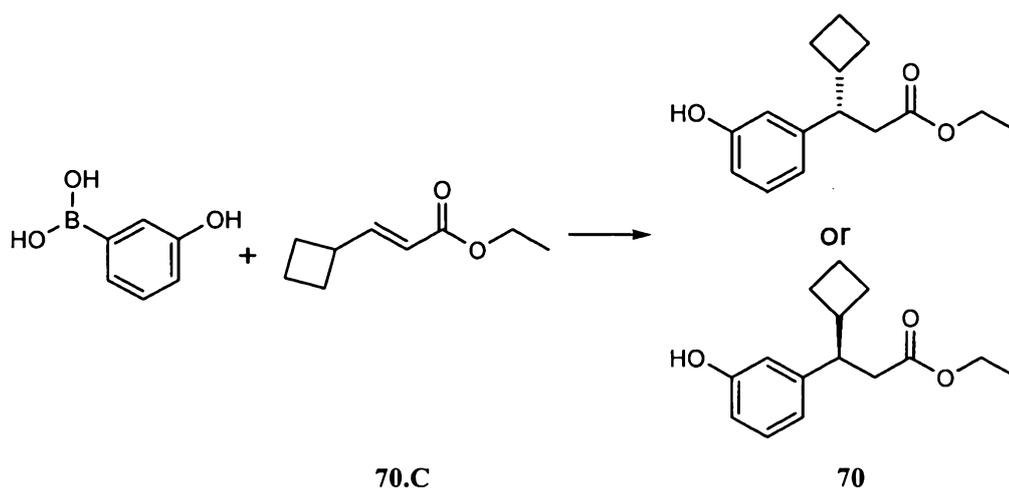


[01101] **Cyclobutanecarbaldehyde (70.B)**. To a solution of cyclobutylmethanol (available from Aldrich)(3.29 mL, 34.8 mmol) in 3:1 MeCN/DCM (80 mL) was added TEMPO (0.272 g, 1.74 mmol) and iodobenzene diacetate (11.8 g, 36.6 mmol) as solids. The resulting slurry was stirred overnight at room temperature to afford a homogeneous solution. The reaction mixture was used directly in the next step.



[01102] **(E)-Ethyl 3-cyclobutylacrylate (70.C)**. To a suspension of lithium chloride (2.22 g, 52.2 mmol) in MeCN (80 mL) were added ethyl 2-(diethoxyphosphoryl)acetate (available from Aldrich)(8.37 mL, 41.8 mmol) and DBU

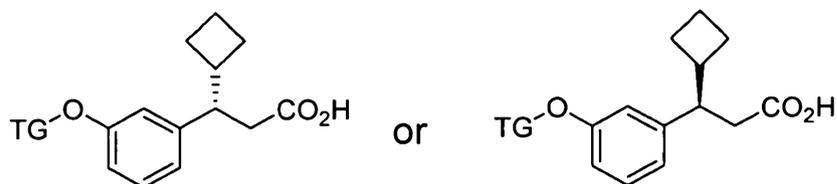
(16.7 mL, 111 mmol) at room temperature. The mixture was cooled to 0°C, and to it was added cyclobutanecarbaldehyde **70.B** (2.93 g, 34.8 mmol) dropwise. The resulting cloudy mixture was warmed to room temperature and stirred overnight. The mixture was partitioned between water and EtOAc. The layers were separated, and the aqueous phase was extracted with additional EtOAc. The combined organic layers were washed with water and brine, dried (MgSO₄), and concentrated. The residue was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to afford (E)-ethyl 3-cyclobutylacrylate **70.C** as a colorless liquid (5.00 g, 94%).



[01103] Methyl (3S)-3-cyclobutyl-3-(3-hydroxyphenyl)propanoate or methyl (3R)-3-cyclobutyl-3-(3-hydroxyphenyl)propanoate (70). A mixture of 3-hydroxyphenylboronic acid (available from Aldrich)(2.2 g, 16 mmol) and hydroxy[(S)-BINAP]-rhodium(I) dimer (0.24 g, 0.16 mmol) in 1,4-dioxane (10 mL, 3.2 mmol) was sparged with N₂. To the mixture were added water (1.0 mL, 3.2 mmol) and (E)-ethyl 3-cyclobutylacrylate **70.C** (0.56 mL, 3.2 mmol). The resulting red-brown solution was warmed to 45°C and stirred for 3 hours (sealed vial). The mixture was cooled to room temperature, diluted with EtOAc, washed with saturated aqueous NaHCO₃ and brine, dried (MgSO₄), and concentrated. The crude product was purified by silica gel flash chromatography (0-25% EtOAc/hexane) to afford (S)-ethyl 3-cyclobutyl-3-(3-hydroxyphenyl)propanoate or (R)-ethyl 3-cyclobutyl-3-(3-hydroxyphenyl)propanoate **70** as a pale yellow oil (0.77g, 96%) (92% e.e.). The enantiomerically enriched mixture was further purified by chiral HPLC (Chiralcel OD, 3% i-PrOH/hexane, 220 nm) to afford **70** as a colorless oil (> 99% e.e.).

[01104] The following compounds were prepared from **70** and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Each of the compounds in the following table were prepared using the same enantiomer of the phenol.

Table 10



Compound	TG	Compound	TG
70.1		70.2	
70.3		70.4	

[01105] (3S)-3-Cyclobutyl-3-(3-(((2-(1,1-dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclobutyl-3-(3-(((2-(1,1-dimethylethyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (**70.1**). MS ESI (neg.) m/e: 471.3 (M-H). ¹H NMR (400 MHz) (CDCl₃) δ ppm 7.59 (1 H, d, J=1.6 Hz), 7.29 (3 H, m), 7.07 (1 H, d, J=7.8 Hz), 6.91 (5 H, m), 6.80 (1 H, d, J=7.4 Hz), 5.07 (2 H, s), 3.83 (3 H, s), 3.02 (1 H, td, J=9.8, 5.5 Hz), 2.67 (1 H, m), 2.53 (1 H, d, J=9.4 Hz), 2.51 (1 H, m), 2.14 (1 H, m), 1.82 (4 H, m), 1.62 (1 H, d, J=10.6 Hz), 1.24 (9 H, s).

[01106] (3S)-3-Cyclobutyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclobutyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (**70.2**). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.39 (dd, 1H), 7.33 (d, 1H), 7.28 (d, 1H), 7.20 (t, 1H), 6.95 (t, 1H), 6.84

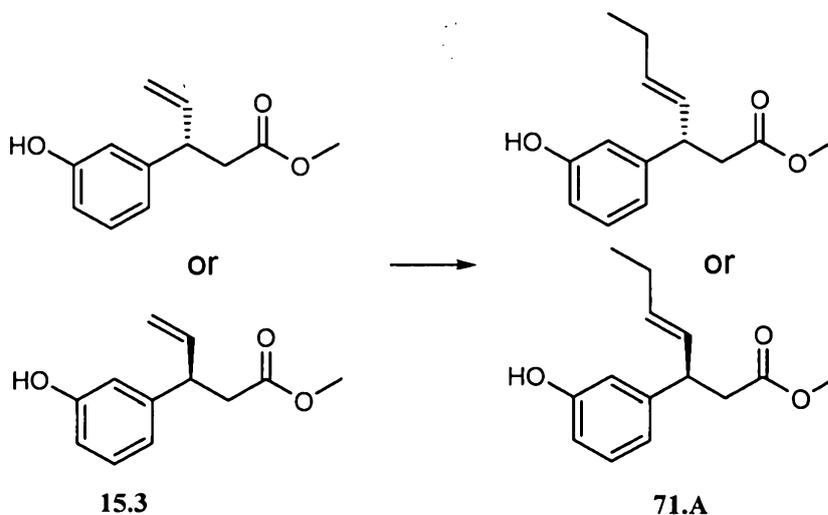
(dd, 1H), 6.78 (m, 4H), 5.52 (bt, 1H), 5.07 (s, 2H), 3.75 (s, 3H), 3.00 (m, 1H), 2.61 (dd, 1H), 2.48 (m, 2H), 2.24 (dt, 2H), 2.08 (m, 1H), 1.73 (m, 4H), 1.65 (t, 2H), 1.58 (m, 1H), 0.85 (s, 6H).

[01107] **(3S)-3-Cyclobutyl-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclobutyl-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (70.3).** ¹H NMR (400 MHz, CDCl₃) δ ppm 7.60 (d, 1H), 7.28 (dd, 1H), 7.21 (t, 1H), 7.04 (d, 1H), 6.99 (t, 1H), 6.81 (m, 5H), 5.06 (s, 2H), 3.78 (s, 3H), 3.00 (m, 1H), 2.61 (dd, 1H), 2.48 (m, 2H), 2.08 (m, 1H), 1.74 (m, 4H), 1.59 (m, 1H), 1.23 (s, 9H).

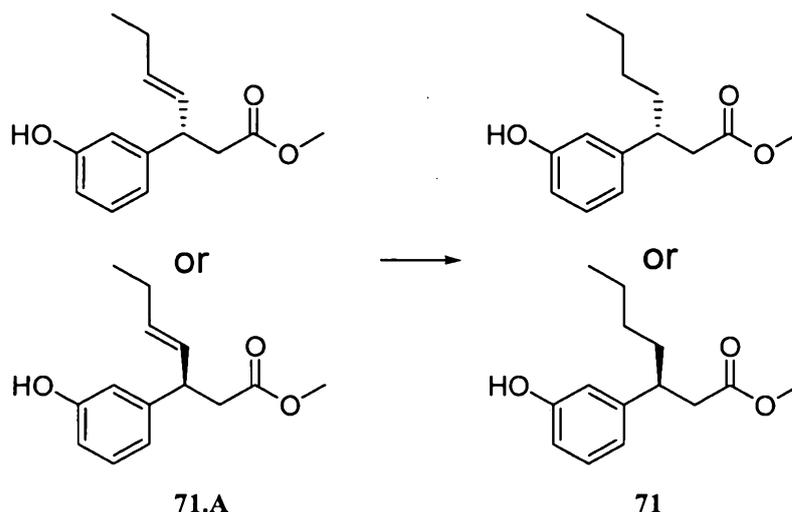
[01108] **(3S)-3-(3-(((2-(Butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclobutylpropanoic acid or (3R)-3-(3-(((2-(butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclobutylpropanoic acid (70.4).** ¹H NMR (400 MHz, CDCl₃) δ ppm 7.28 (d, 1H), 7.20 (t, 1H), 7.06 (m, 2H), 7.02 (t, 1H), 6.88 (dd, 1H), 6.83 (m, 3H), 6.78 (d, 1H), 5.05 (s, 2H), 3.98 (t, 2H), 3.79 (s, 3H), 3.00 (m, 1H), 2.61 (dd, 1H), 2.48 (m, 2H), 2.08 (m, 1H), 1.74 (m, 4H), 1.66 (m, 2H), 1.59 (m, 1H), 1.37 (m, 2H), 0.88 (t, 3H).

[01109] **Example 71**

[01110] **Synthesis of methyl (3R)-3-(3-hydroxyphenyl)heptanoate or methyl (3S)-3-(3-hydroxyphenyl)heptanoate (71).**



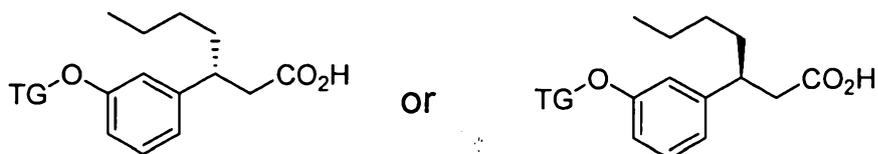
[01111] **(S,E)-Methyl 3-(3-hydroxyphenyl)hept-4-enoate or (R,E)-methyl 3-(3-hydroxyphenyl)hept-4-enoate (71.A).** To a solution of 15.3 (0.10 g, 0.48 mmol) in DCM (1 mL) were added (E)-hex-3-ene (available from Aldrich)(0.90 mL, 7.3 mmol) and Grubbs II catalyst(0.021 g, 0.024 mmol). The mixture was stirred overnight at 40°C (sealed vial), cooled to room temperature, and concentrated. The residue was purified by silica gel flash chromatography (0-25% EtOAc/hexane) to afford 71.A as a pale yellow oil (110 mg, 97%).



[01112] **Methyl (3R)-3-(3-hydroxyphenyl)heptanoate or methyl (3S)-3-(3-hydroxyphenyl)heptanoate).** A vial containing a solution of 71.A (91 mg, 388 μ mol) in EtOAc (1.5 mL) was purged with N₂, and to it was added 10% Pd/C (21 mg, 19 μ mol). The vial was then purged with H₂ and the contents stirred overnight under a H₂ balloon. The black mixture was flushed through a pad of silica gel (EtOAc) and concentrated. The residue was purified by silica gel flash chromatography (0-25% EtOAc/hexane) to afford (R)-methyl 3-(3-hydroxyphenyl)heptanoate or (S)-methyl 3-(3-hydroxyphenyl)heptanoate as a colorless oil (81 mg, 88%).

[01113] The following compounds were prepared from 71 and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Each of the compounds in the following table were prepared using the same enantiomer of the phenol.

Table 11



Compound	TG	Compound	TG
71.1		71.2	
71.3			

[01114] (3R)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)heptanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)heptanoic acid.1).

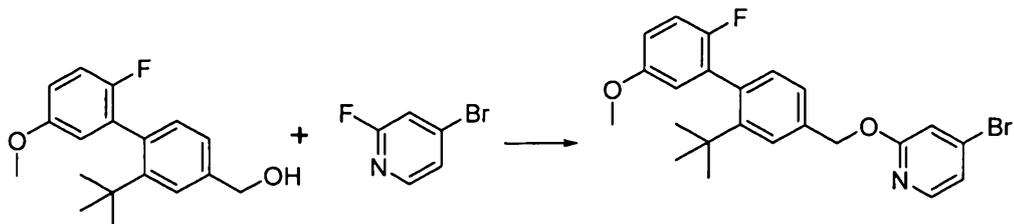
MS ESI (pos.) m/e: 493.3 (M+H)⁺, 510.2 (M+H₂O)⁺, 515.2 (M+Na)⁺.

[01115] (3R)-3-(3-(((2-(Butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)heptanoic acid or (3S)-3-(3-(((2-(butyloxy)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)heptanoic acid (71.2). MS ESI

(pos.) m/e: 509.2 (M+H)⁺, 526.3 (M+H₂O)⁺, 531.2 (M+Na)⁺, 547.2 (M+K)⁺.

[01116] (3R)-3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)heptanoic acid or (3S)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)heptanoic acid (71.3). MS ESI (pos.) m/e: 548.3 (M+H₂O)⁺.

[01117] Example 72

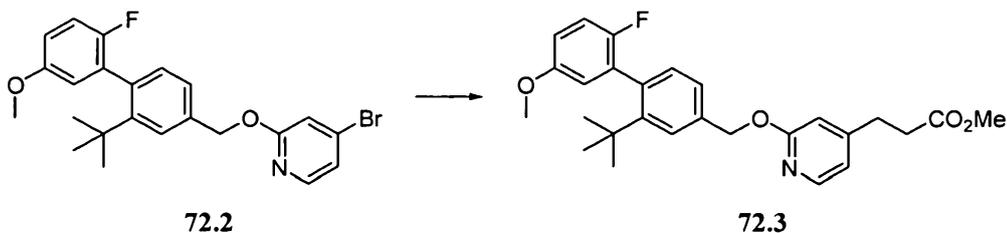


8.9

72.1

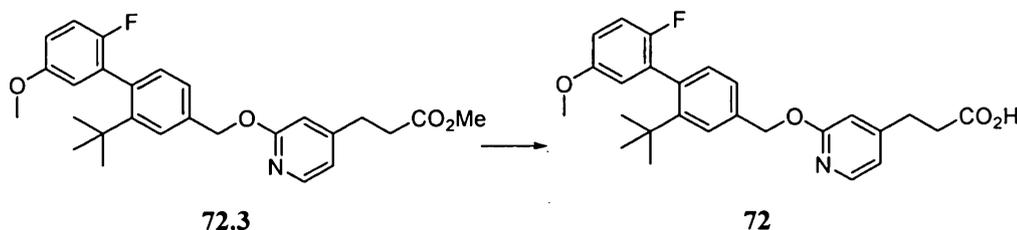
72.2

[01118] **4-Bromo-2-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)pyridine (72.2)**. A dry round bottom flask containing **8.9** (0.0889 g, 0.308 mmol) in dry DMF (1.5 mL) was cooled in an ice bath. After about 10 minutes, sodium hydride (0.0150 g, 0.375 mmol) (60% wt in oil) was added carefully, and the mixture was stirred at 0°C. After 10 minutes, **72.1** (commercially available from Synthonix Corporation) (0.0543 g, 0.308 mmol) was added. The reaction was allowed to stir overnight at room temperature. After 18 hours, the reaction was diluted with water and then extracted five times with EtOAc. The organic extracts were then washed one time with brine and dried over anhydrous MgSO₄. The solid was filtered off, and the solvent was concentrated. The residue was purified by flash chromatography (SiO₂ gel 60, eluted with 0 to 25% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **72.2** as a colorless oil (0.0993 g, 73%). ¹H NMR (400 MHz) (CDCl₃) δ ppm 8.07 (1 H, m), 7.66 (1 H, d, J=1.6 Hz), 7.32 (1 H, dd, J=7.8, 1.6 Hz), 7.10 (3 H, m), 7.02 (1H, t, J= 8.8 Hz), 6.87 (1 H, dt, J= 8.9, 3.6 Hz), 6.81 (1 H, dd, J=5.9, 3.1 Hz), 5.43 (2 H, s), 3.80 (3 H, s), 1.27 (9 H, s).



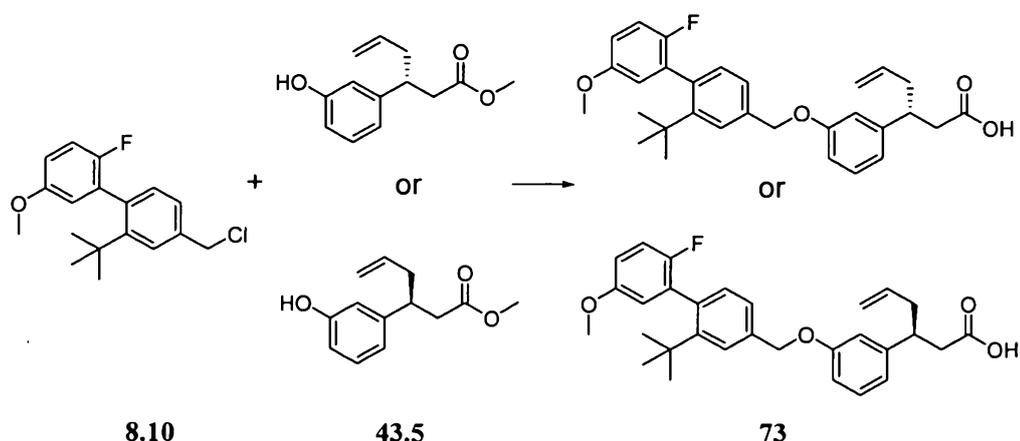
[01119] **Methyl 3-(2-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-4-pyridinyl)propanoate (72.3)**. To a sealed tube containing **72.2** (0.0980 g, 0.22 mmol), bis(dibenzylideneacetone)palladium (0.0068 g, 0.012 mmol), and CTC-Q-Phos (commercially available from Strem Chemicals.) (0.0083 g, 0.0116 mmol) was added dry THF (3.000 mL, 0.22 mmol). After about 5 minutes, 3-ethoxy-3-oxopropylzinc bromide, 0.5M solution in THF (1.000 mL, 0.50 mmol) was added dropwise. After 1 hour, the mixture was heated to 80°C and monitored with TLC and LC-MS. After 16.5 hours, the reaction was cooled to room temperature and the organic solvent was then removed under reduced pressure. The residue was purified by flash chromatography (SiO₂ gel 60, eluted with 0 to 40% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to a light brown oil

(0.0646 g, 63%). ¹H NMR (400 MHz) (CDCl₃) δ ppm 8.11 (1 H, d, J=5.3 Hz), 7.65 (1 H, d, J=1.6 Hz), 7.32 (1 H, dd, J=7.7, 1.7 Hz), 7.07 (2 H, m), 6.85 (1 H, dt, J=8.9, 3.6 Hz), 6.80 (2 H, m), 6.70 (1 H, s), 5.41 (2 H, s), 4.15 (2 H, q, J=7.2 Hz), 3.79 (3 H, s), 2.93 (2 H, t, J=7.6 Hz), 2.64 (2 H, t, J=7.7 Hz), 1.29 (12 H, m).



[01120] **3-(2-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-4-pyridinyl)propanoic acid (72).** Ester 72.3 was hydrolyzed by the methods reported in US 2006/0004012 to perform such operations on other compounds. MS ESI (neg.) m/e: 436.1 (M-H). ¹H NMR (400 MHz) (CDCl₃) δ ppm 8.21 (1 H, d, J=5.5 Hz), 7.63 (1 H, d, J=1.6 Hz), 7.30 (2 H, dd, J=7.6, 1.8 Hz), 7.08 (2 H, m), 6.91 (1 H, m), 6.87 (1 H, m), 6.80 (1 H, s), 6.77 (1 H, dd, J=5.9, 3.1 Hz), 5.40 (2 H, s), 3.79 (3 H, s), 2.98 (2 H, t, J=7.4 Hz), 2.73 (2 H, t, J=7.4 Hz), 1.24 (9 H, s).

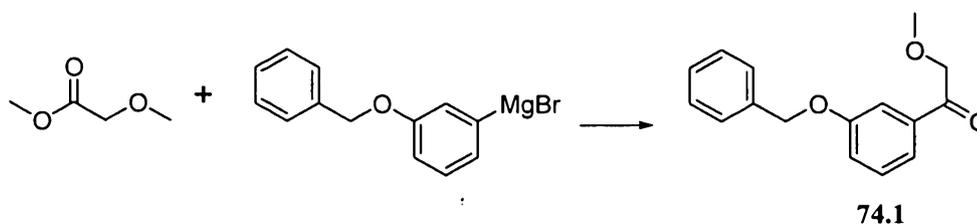
[01121] **Example 73**



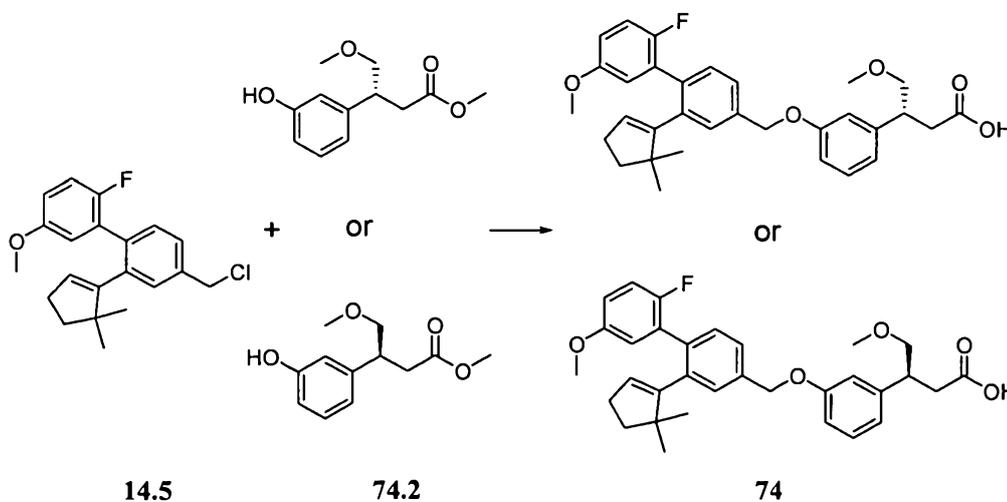
[01122] **(3S)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-5-hexenoic acid or (3R)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-5-hexenoic acid (73).** Compound 43.5 was coupled with 8.10 and hydrolyzed according to the methods described herein. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.60 (d, 1H), 7.29 (dd,

1H), 7.24 (t, 1H), 7.05 (d, 1H), 6.99 (t, 1H), 6.85 (m, 4H), 6.77 (dd, 1H), 5.65 (m, 1H), 5.07 (s, 2H), 5.00 (m, 2H), 3.78 (s, 3H), 3.19 (m, 1H), 2.72 (dd, 1H), 2.61 (dd, 1H), 2.39 (m, 2H), 1.23 (s, 9H).

[01123] Example 74



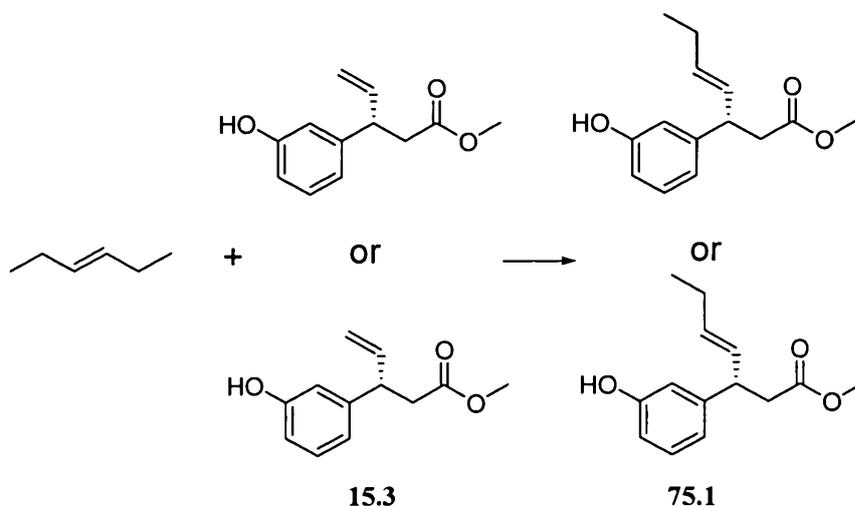
[01124] 1-(3-(Benzyloxy)phenyl)-2-methoxyethanone (74.1). To a solution of methyl methoxyacetate (available from Aldrich)(0.48 mL, 4.8 mmol) in ether (20.0 mL) was added a 1.0 M solution of (3-(benzyloxy)phenyl)magnesium bromide in THF (available from Aldrich)(5.0 mL, 5.0 mmol) dropwise at -78 °C. The mixture was warmed to room temperature overnight, quenched with 1 N HCl, and diluted with EtOAc. The organics were washed with water and brine, dried (MgSO₄), and concentrated. The crude product was purified by silica gel flash chromatography (0-20% EtOAc/hexane) to afford 1-(3-(benzyloxy)phenyl)-2-methoxyethanone (0.17 g, 14%) as a pale yellow oil.



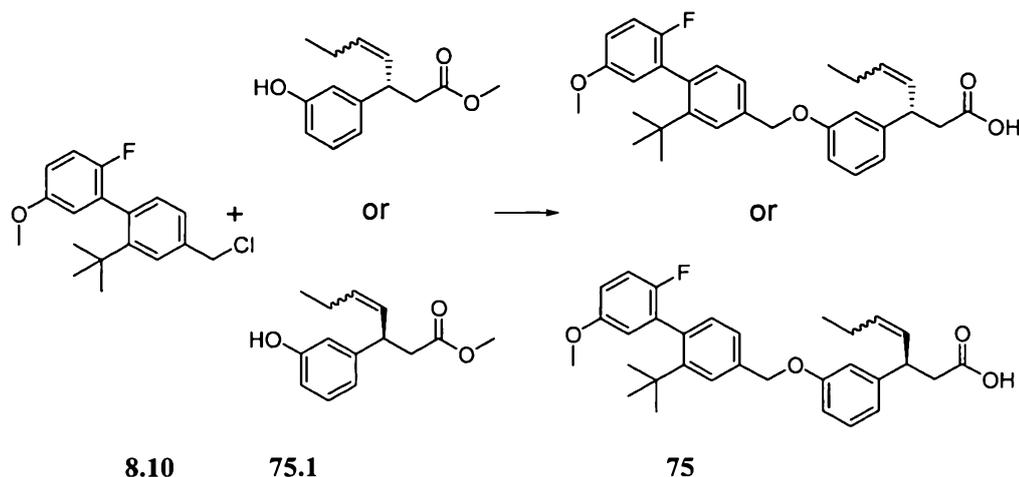
[01125] (3R)-3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-(methoxy)butanoic acid or (3S)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-

biphenyl-4-yl)methyl)oxy)phenyl)-4-(methoxy)butanoic acid (74). Compound **74.2** was obtained from compound **74.1** by a method analogous to that used for the preparation of compound **5.7** as described in Example **5** using a Peterson olefination followed by hydrogenation and final chiral separation. Coupling with **14.5** and hydrolysis was carried out according to the methods described herein. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 7.39 (dd, 1H), 7.33 (d, 1H), 7.28 (d, 1H), 7.24 (t, 1H), 6.96 (t, 1H), 6.88 (m, 2H), 6.84 (bd, 1H), 6.79 (m, 2H), 5.52 (bt, 1H), 5.08 (s, 2H), 3.75 (s, 3H), 3.56 (dd, 1H), 3.48 (t, 1H), 3.40 (m, 1H), 3.33 (s, 3H), 2.88 (dd, 1H), 2.65 (dd, 1H), 2.24 (dt, 2H), 1.65 (t, 2H), 0.85 (s, 6H).

[01126] **Example 75**



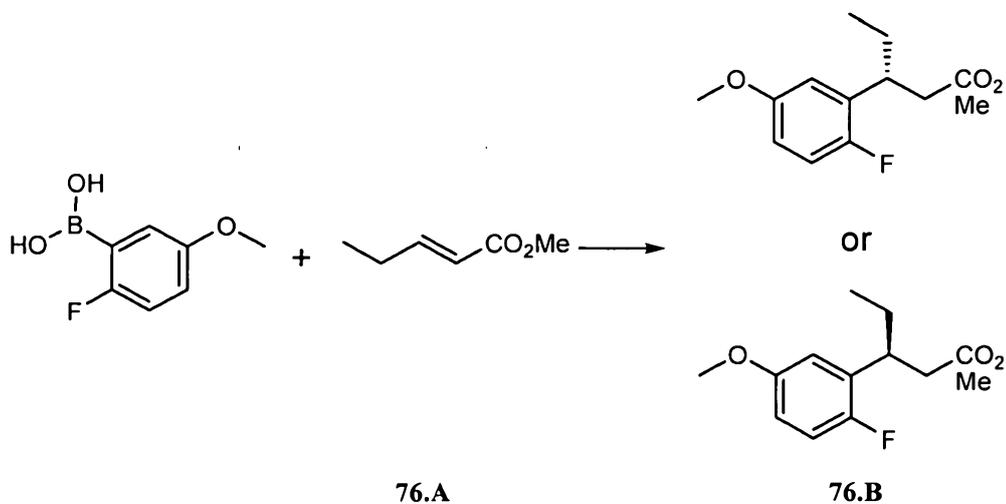
[01127] **Methyl (3S,4E)-3-(3-hydroxyphenyl)-4-heptenoate or methyl (3R,4E)-3-(3-hydroxyphenyl)-4-heptenoate (75.1).** To a solution of **15.3** (0.10 g, 0.48 mmol) in DCM (1 mL), were added (E)-hex-3-ene (available from Aldrich)(0.90 mL, 7.3 mmol) and Grubbs Catalyst 2nd Generation (0.021 g, 0.024 mmol). The mixture was stirred overnight at 40 °C, cooled to room temperature, and concentrated. The crude product was purified by silica gel flash chromatography (0-25% EtOAc/hexane) to afford **75.1** (0.11 g, 97%) as a pale yellow oil.



[01128] (3S)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-heptenoic acid or (3R)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-heptenoic acid (75). Coupling of 75.1 with 8.10 and hydrolysis was carried out according to the methods described herein. MS ESI (pos.) m/e: 491.2 (M+H)⁺, 508.3 (M+H₂O)⁺, 513.3 (M+Na)⁺.

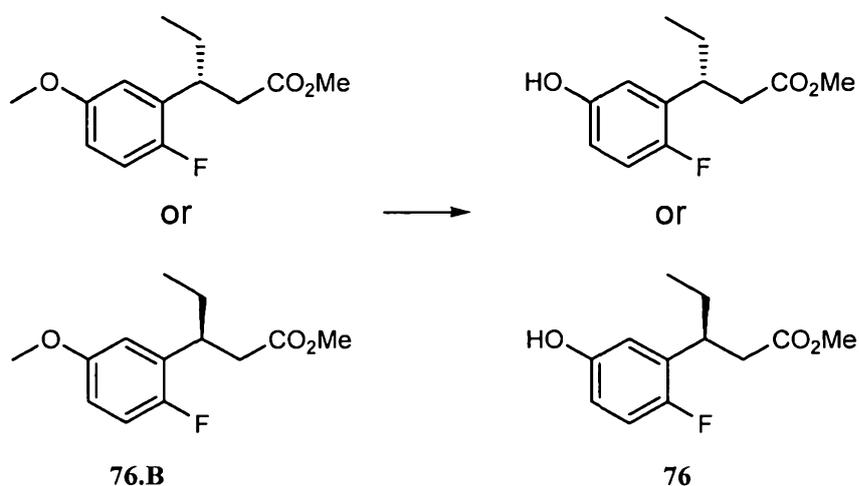
[01129] **Example 76**

[01130] Synthesis of methyl (3R)-3-(2-fluoro-5-hydroxyphenyl)pentanoate or methyl (3S)-3-(2-fluoro-5-hydroxyphenyl)pentanoate (76).



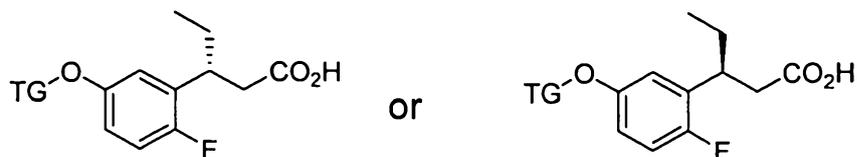
[01131] (R)-Methyl 3-(2-fluoro-5-methoxyphenyl)pentanoate or (S)-methyl 3-(2-fluoro-5-methoxyphenyl)pentanoate (76.B). A dioxane/water (10/1 mixture (5.5

mL)) mixture was added to a flask charged with hydroxy[(S)-BINAP]-rhodium(I) dimer (260 mg, 175 μ mol) and 2-fluoro-5-methoxyphenylboronic acid (commercially available from Aldrich)(3.0 g, 17522 μ mol) and (E)-methyl pent-2-enoate (available from Aldrich)(400 mg, 3504 μ mol). The mixture was flushed with nitrogen. The resulting mixture was then stirred at 40°C for 3 hours. After removal of the solvent, the residue was dissolved in EtOAc. The solution was washed with water, brine and dried over anhydrous Na₂SO₄. The crude was purified by silica gel flash chromatography (0 to 15% EtOAc/Hexanes) to provide (R)-methyl 3-(2-fluoro-5-methoxyphenyl)pentanoate or (S)-methyl 3-(2-fluoro-5-methoxyphenyl)pentanoate **76.B** (167 mg, 20% yield) as a colorless oil. The product is believed to be the R enantiomer.



[01132] Methyl (3R)-3-(2-fluoro-5-hydroxyphenyl)pentanoate or methyl (3S)-3-(2-fluoro-5-hydroxyphenyl)pentanoate (76). To a solution of **76.B** (167 mg, 695 μ mol) in DCE (5 mL) was added 1,2-ethanedithiol (932 μ L, 11121 μ mol) followed by anhydrous aluminum chloride (741 mg, 5560 μ mol) at 0°C. The reaction mixture was allowed to slowly warm to room temperature over four hours and then quenched with saturated Rochelle's salt solution. The mixture was extracted (2 x 50 mL) with DCM. The combined organic layers were washed with water (1 x 40 mL) and brine (1 x 40 mL) and dried over magnesium sulfate. The filtrate was concentrated, and the residue was purified by chromatography (silica, 0 to 30% EtOAc:hexanes) to give **76** (100mg, 75%)

[01133] The following compounds were prepared from **76** and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Each of the compounds in the following table were prepared using the same enantiomer of the phenol.

Table 12

Compound	TG	Compound	TG
76.1		76.2	
76.3	 or 		

[01134] (3R)-3-(5-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3S)-3-(5-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid (76.1). (MS ESI (neg.) m/e: 519.2 (M-H)).

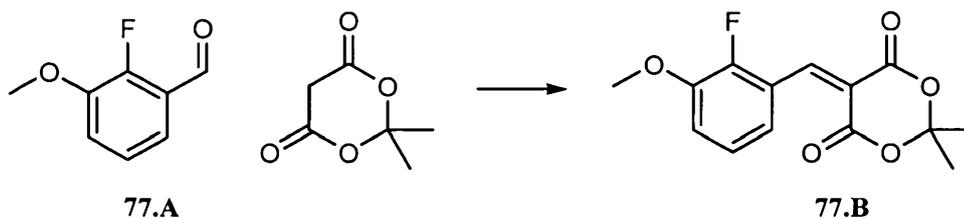
[01135] (3R)-3-(5-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3S)-3-(5-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid (76.2). (MS ESI (neg.) m/e: 481.2 (M-H)).

[01136] (3R)-3-(5-(((2-((1S)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3R)-3-(5-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-

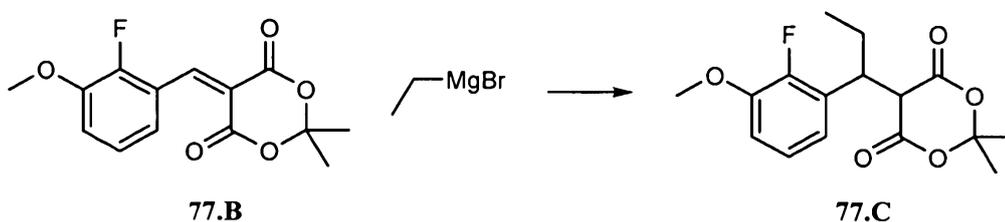
yl)methyloxy)-2-fluorophenyl)pentanoic acid or (3S)-3-(5-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyloxy)-2-fluorophenyl)pentanoic acid or (3S)-3-(5-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyloxy)-2-fluorophenyl)pentanoic acid (76.3). MS ESI (neg.) m/e: 521.3 (M-H)

[01137] **Example 77**

[01138] **Synthesis of methyl (3R)-3-(2-fluoro-3-hydroxyphenyl)pentanoate and methyl (3S)-3-(2-fluoro-3-hydroxyphenyl)pentanoate (77.G and 77.H).**

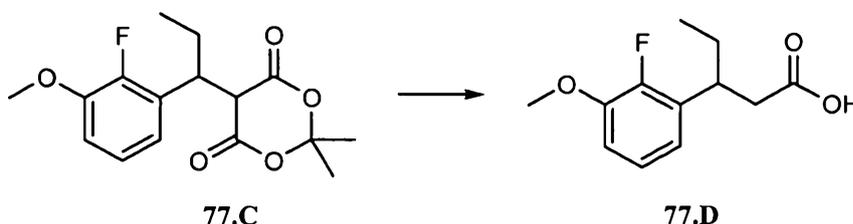


[01139] **5-(2-Fluoro-3-methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (77.B).** A 500 mL round bottom flask was charged with 2-fluoro-3-methoxybenzaldehyde 77.A (available from Aldrich)(28.6 g, 186 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione (available from Aldrich)(34.8 g, 241 mmol), and water (350 mL). The heterogeneous mixture was stirred for 2 hours at 90°C (reflux), cooled to room temperature, and filtered. The resulting off-white solid was triturated with ether to afford 5-(2-fluoro-3-methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione 77.B (30.6 g, 58.8% yield) as a crystalline white powder.

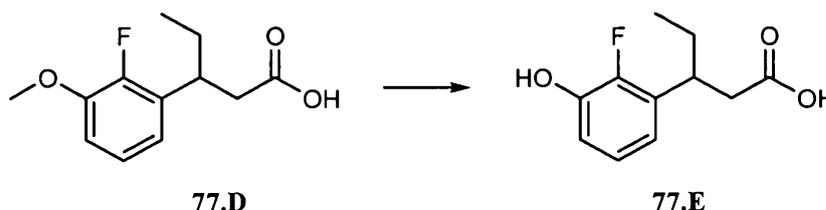


[01140] **5-(1-(2-Fluoro-3-methoxyphenyl)propyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (77.C).** A 500 mL round bottom flask was charged with 5-(2-fluoro-3-methoxybenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione 77.B (5.00 g, 17.8 mmol) and THF (100 mL). The resulting slurry was cooled to 0°C, and to it was added ethylmagnesium bromide (available from Aldrich)(3.0 M/ether) (11.9 mL, 35.7 mmol) dropwise over 15 minutes. The cooling bath was removed, and the mixture was stirred for 1 hour at ambient temperature. The reaction was quenched with 1 N HCl and

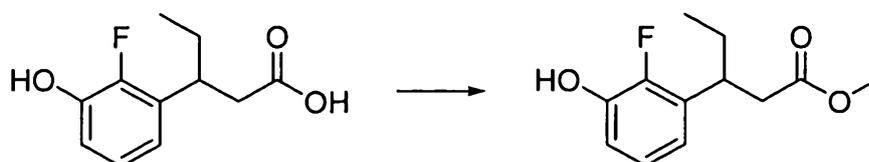
extracted with EtOAc. The combined organic layers were washed with brine, dried (MgSO₄), and concentrated to afford 5-(1-(2-fluoro-3-methoxyphenyl)propyl)-2,2-dimethyl-1,3-dioxane-4,6-dione **77.C** (5.17 g, 93.4% yield) as a yellow oil (5.2 g, 93%). The product thus obtained was used without further purification.



[01141] 3-(2-Fluoro-3-methoxyphenyl)pentanoic acid (77.D). A 500 mL round bottom flask was charged with 5-(1-(2-fluoro-3-methoxyphenyl)propyl)-2,2-dimethyl-1,3-dioxane-4,6-dione **77.C** (5.17 g, 16.7 mmol) and 10:1 DMF/water (80 mL). The pale yellow solution was stirred overnight at 90°C, cooled to room temperature, and diluted with ether. The combined organic layers were washed with water and brine, dried (MgSO₄), and concentrated to afford 3-(2-fluoro-3-methoxyphenyl)pentanoic acid **77.D** (3.44 g, 91.3% yield) as a yellow oil. The crude product was used without further purification.



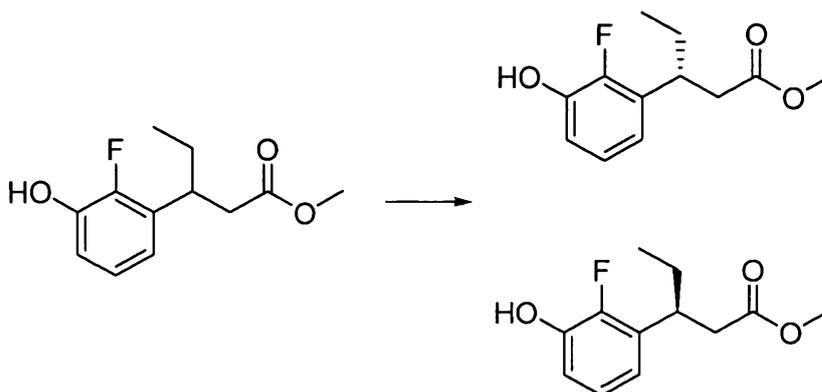
[01142] 3-(2-Fluoro-3-hydroxyphenyl)pentanoic acid (77.E). A 500 mL round bottom flask was charged with 3-(2-fluoro-3-methoxyphenyl)pentanoic acid **77.D** (3.44 g, 15.2 mmol), NMP (30 mL), NaOH (2.74 g, 68.4 mmol), and 1-dodecanethiol (available from Aldrich)(12.8 mL, 53.2 mmol). The mixture was stirred for 5 hours at 125°C under N₂, cooled to room temperature, and diluted with 1 N HCl and EtOAc. The combined organic layers were washed with water and brine, dried (MgSO₄), and concentrated to afford 3-(2-fluoro-3-hydroxyphenyl)pentanoic acid **77.E** as a yellow liquid (3.23g). The product so obtained was used without further purification.



77.E

77.F

[01143] **Methyl 3-(2-fluoro-3-hydroxyphenyl)pentanoate (77.F)**. A 500 mL round bottom flask was charged with 77.E (21.5 g, 101 mmol), MeOH (300 mL), and sulfuric acid (1.08 mL, 20.3 mmol). The solution was stirred for 1 hour at 80°C, cooled to room temperature, and diluted with ether. The organic layers were washed with saturated aqueous NaHCO₃, water, and brine, dried (MgSO₄), and concentrated. The crude product was purified by silica gel flash chromatography (0-30% EtOAc/hexane) to afford 77.F (20.6 g, 90% yield) as a yellow oil.

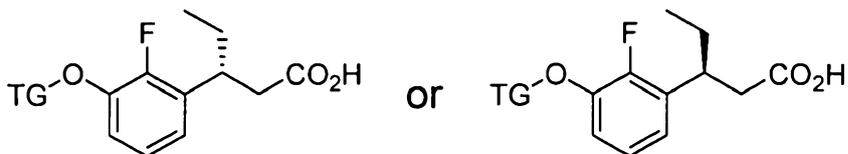


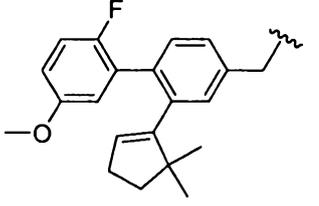
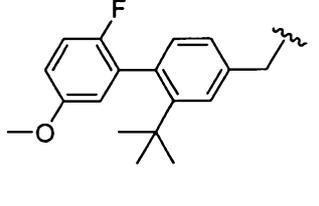
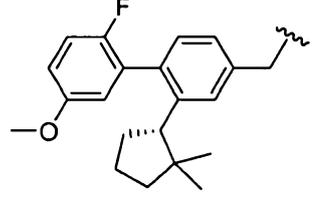
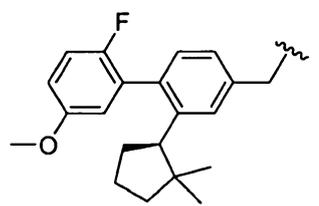
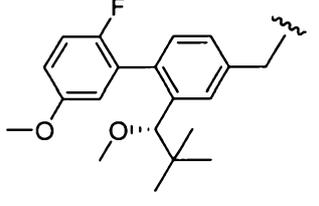
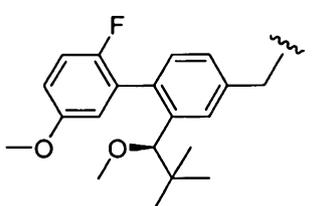
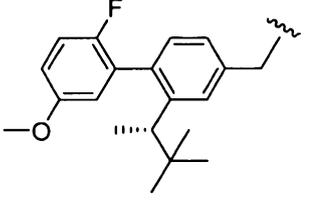
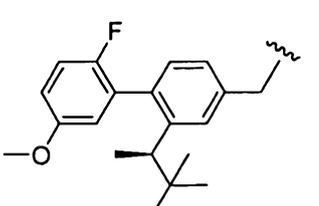
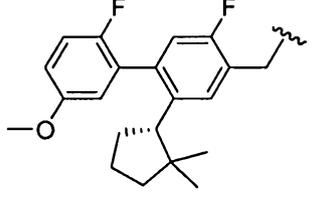
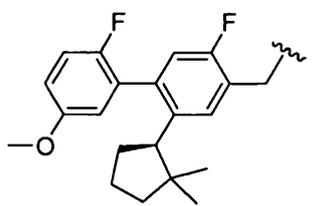
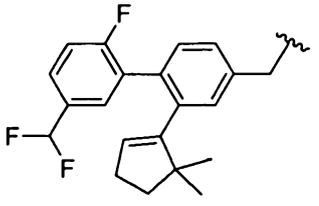
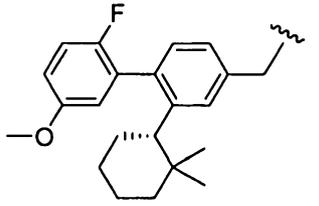
77.F

77.G and 77.H

[01144] **(R)-Methyl 3-(2-fluoro-3-hydroxyphenyl)pentanoate and (S)-methyl 3-(2-fluoro-3-hydroxyphenyl)pentanoate (77.G and 77.H)**. Racemic 77.F (20 g) was resolved by chiral HPLC (Chiralcel OD column, 3% IPA/hexane, detection at 220 nm) to afford (in order of elution) 77.G (8 g, 80% yield, 99% e.e.) and 77.H (8 g, 80% yield, 99% e.e.) as colorless oils.

[01145] The following compounds were prepared from 77.G and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Each of the compounds in the following table were prepared using the same enantiomer of the phenol.

Table 13

Compound	TG	Compound	TG
77.1		77.2	
77.3	 <p style="text-align: center;">or</p> 	77.4	 <p style="text-align: center;">or</p> 
77.5	 <p style="text-align: center;">or</p> 	77.6	 <p style="text-align: center;">or</p> 
77.7		77.8	 <p style="text-align: center;">or</p>

Compound	TG	Compound	TG
77.9		77.10	
	or		or
77.11		77.12	

[01146] (3R)-3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3S)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid (77.1). (MS ESI (neg.) m/e: 519.2 (M-H)).

[01147] (3R)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid (77.2). (MS ESI (neg.) m/e: 481.2 (M-H)).

[01148] (R)-3-{3-[2-((S)-2,2-Dimethyl-cyclopentyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-2-fluoro-phenyl}-pentanoic acid or (S)-3-{3-[2-((S)-2,2-dimethyl-cyclopentyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-2-fluoro-

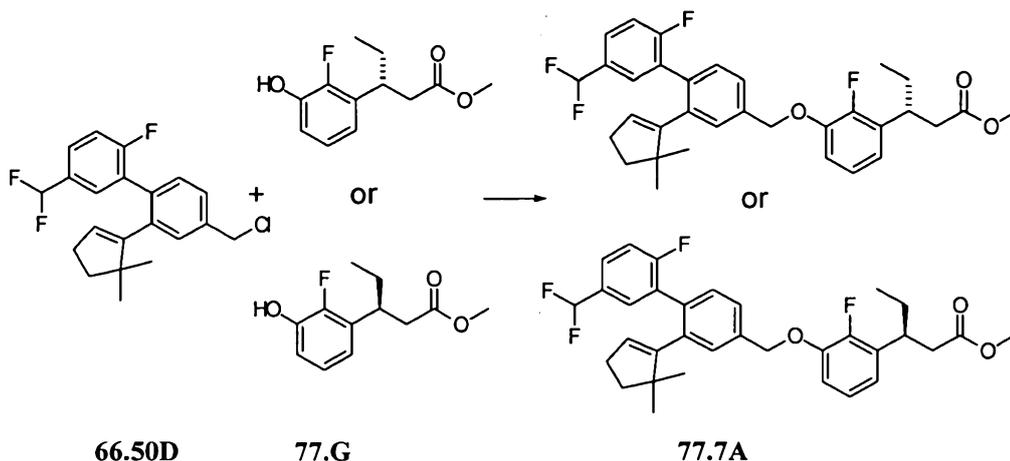
phenyl}-pentanoic acid or (S)-3-{3-[2-((R)-2,2-dimethyl-cyclopentyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-2-fluoro-phenyl}-pentanoic acid or (R)-3-{3-[2-((R)-2,2-Dimethyl-cyclopentyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-2-fluoro-phenyl}-pentanoic acid (77.3). MS ESI (neg.) m/e: 521.2 (M-H).

[01149] (3R)-3-(3-(((2-((1S)-2,2-Dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid (77.4). MS ESI (neg.) m/e: 525.3 (M-H).

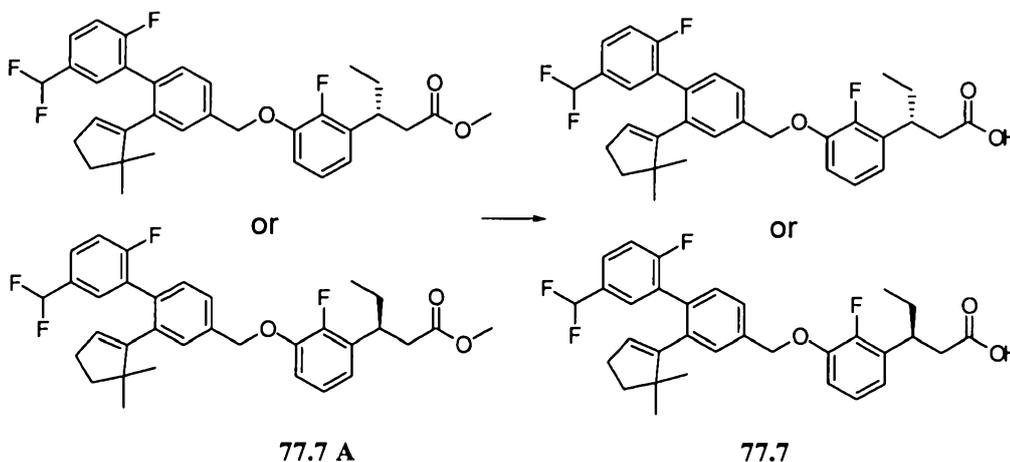
[01150] (3R)-3-(2-Fluoro-3-(((2'-fluoro-5'-(methoxy)-2-((1S)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3R)-3-(2-fluoro-3-(((2'-fluoro-5'-(methoxy)-2-((1R)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(2-fluoro-3-(((2'-fluoro-5'-(methoxy)-2-((1S)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(2-fluoro-3-(((2'-fluoro-5'-(methoxy)-2-((1R)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid (77.5). MS ESI (neg.) m/e: 509.2 (M-H).

[01151] (3R)-3-(3-(((2-((1S)-2,2-Dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid (77.6). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 66.44D derived from peak one from the chiral separation of 66.44A from the OJ-column, also using 77.G derived from peak one from the chiral separation of the racemic ester 77.F, described herein) to yield 77.6. MS ESI (neg.) m/e: 538.9 (M-H)⁺.

[01152] Example 77.7



[01153] **Methyl (3R)-3-(3-(((5'-(difluoromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoate or methyl (3S)-3-(3-(((5'-(difluoromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoate (77.7A).** To a vial containing 77.G (0.0249 g, 0.110 mmol) in 1.00 mL dry DMF was added cesium carbonate (0.0434 g, 0.133 mmol). The mixture was stirred at room temperature for 10 minutes, then 66.50D (0.0444 g, 0.122 mmol) was added. After 22 hours, the reaction was diluted with water and then extracted five times with EtOAc. The organic layers were combined and washed one time with brine and dried over anhydrous magnesium sulfate. The solid was filtered off, and the solvent was removed. The residue was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to afford 77.7A (54.6 mg, 89% yield). MS ESI (pos.) m/e: 571.9 (M+H₂O)⁺.



[01154] (3R)-3-(3-(((5'-(Difluoromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3S)-3-(3-(((5'-(difluoromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid (77.7). A pre-mixed solution of 2 M NaOH (0.5 mL, 1.00 mmol), THF (1 mL), and MeOH (1 mL) was added to a vial containing 77.7A (0.0546 g, 0.0984 mmol). The mixture was stirred at room temperature and monitored with TLC and LC-MS. After 24 hours, the mixture was diluted with water and acidified with 1M aqueous HCl solution, and then was extracted five times with EtOAc. The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel flash chromatography (0-40% EtOAc/hexane) to afford 77.7 (31.3 mg, 59% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.48 (3 H, m), 7.37 (2 H, m), 7.15 (1 H, t, J=9.0 Hz), 7.04 (1 H, m), 6.95 (1 H, m), 6.83 (1 H, m), 6.77 (1H, t), 5.52 (1 H, m), 5.18 (2 H, s), 3.43 (1 H, m), 2.77 (2 H, m), 2.23 (2 H, td, J=7.0, 2.3 Hz), 1.84 (4 H, m), 0.86 (9 H, m). MS ESI (neg.) m/e: 538.9 (M-H)⁺.

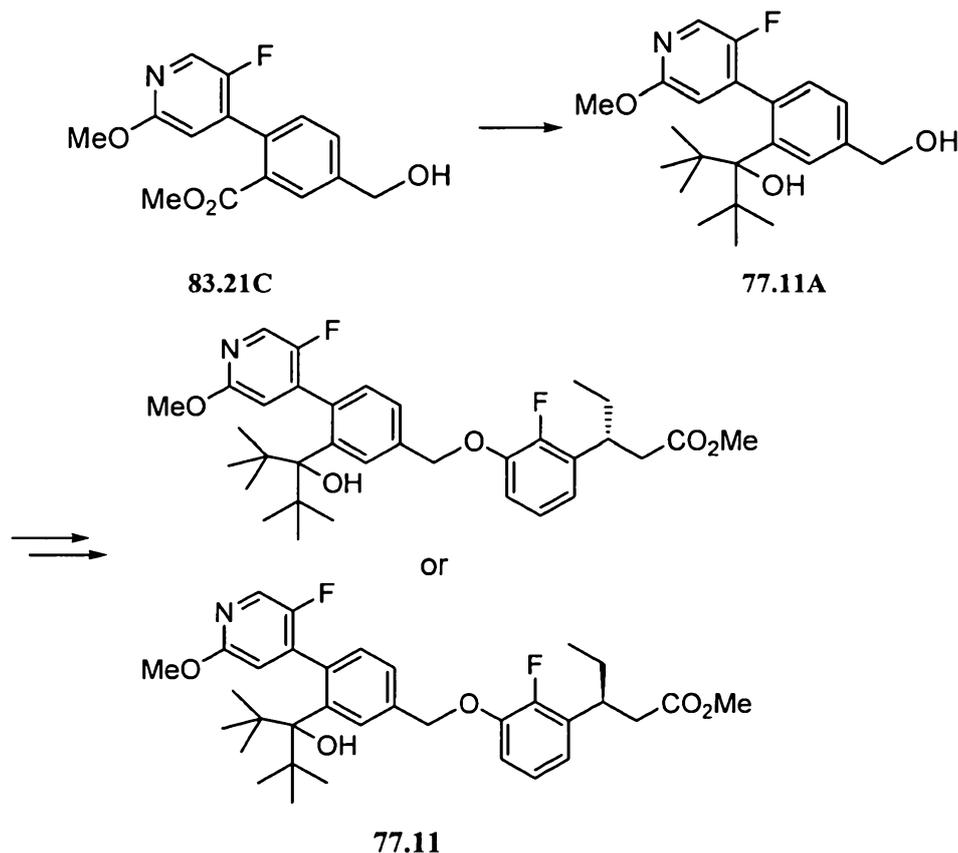
[01155] (3R)-3-(3-(((2-((1S)-2,2-Dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid (77.8). MS ESI (neg.) m/e: 535.3 (M-H)⁺.

[01156] (3R)-3-(3-(((3-((1S)-2,2-Dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3R)-3-(3-(((3-((1R)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3S)-3-(3-(((3-((1S)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3S)-3-(3-(((3-((1R)-2,2-Dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)pentanoic acid (77.9). MS ESI (neg.) m/e: 522.2 (M-H)⁺.

[01157] (3R)-3-(3-(((3-((1S)-2,2-Dimethyl-1-(methoxy)propyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3R)-3-(3-(((3-((1R)-2,2-dimethyl-1-(methoxy)propyl)-4-(5-fluoro-2-(methoxy)-4-

pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3S)-3-(3-(((3-((1S)-2,2-dimethyl-1-(methoxy)propyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3S)-3-(3-(((3-((1R)-2,2-dimethyl-1-(methoxy)propyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)pentanoic acid (77.10). (MS ESI) (pos) m/e: 528.3 (M+H).

[01158] **Example 77.11**

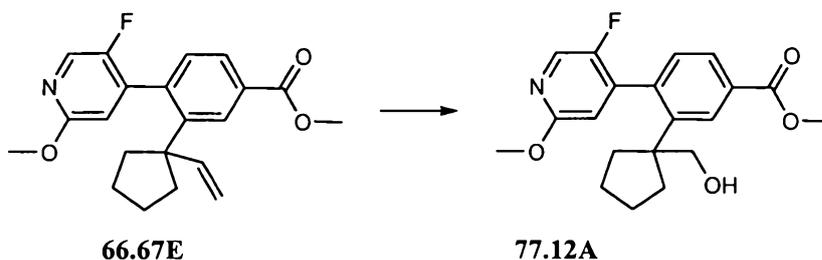


[01159] (3R)-3-(3-(4-(5-Fluoro-2-methoxy-4-pyridinyl)-3-(3-hydroxy-2,2,4,4-tetramethylpentan-3-yl)benzyloxy)-2-fluorophenyl)pentanoic acid or (3R)-3-(3-(4-(5-fluoro-2-methoxy-4-pyridinyl)-3-(3-hydroxy-2,2,4,4-tetramethylpentan-3-yl)benzyloxy)-2-fluorophenyl)pentanoic acid (77.11). To a -78°C solution of methyl 2-(5-fluoro-2-methoxy-4-pyridinyl)-5-(hydroxymethyl)benzoate (83.21C) (233 mg, 8.0 mol) in THF (60 mL) was added tert-butyllithium (1.70 M, 1.65 mL, 2.80 mmol) dropwise over one hour. After stirring at -78°C for 40 minutes, the resulting mixture was slowly poured into 4 mL of saturated aqueous ammonium chloride solution. After separation,

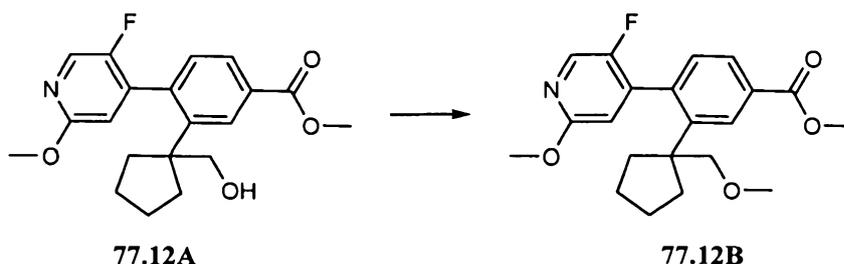
the aqueous layer was diluted with water (40 mL) and extracted with EtOAc (3 x 6 mL). The combined organic layers were washed with water (4 mL) and brine (2 mL). After removal of organic solvents under reduced pressure, purification of the residue by flash chromatography on silica gel with 0-75% EtOAc/Hexane for elution gave **77.11A** as colorless solid (96 mg, 32%).

[01160] The Mitsunobu reaction and hydrolysis were conducted in an analogous manner to Example **69.14** (using **77.11A** and using **77.G** derived from peak one from the chiral separation of the racemic ester **77.F**, described herein) to yield **77.11** (MS ESI (neg.) m/e: 568.3 (M-H)).

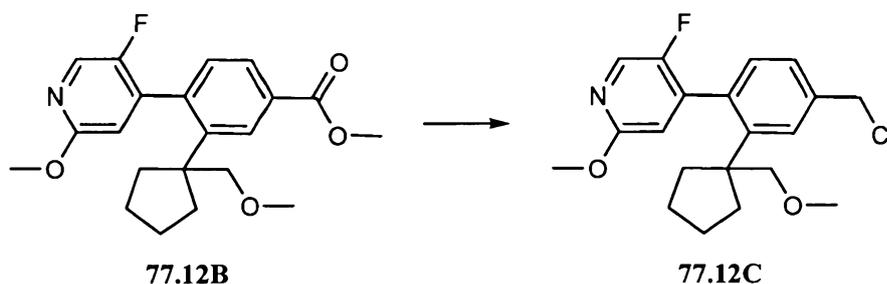
[01161] **Example 77.12**



[01162] **Methyl 4-(5-fluoro-2-methoxypyridin-4-yl)-3-(1-(hydroxymethyl)cyclopentyl)benzoate (77.12A)**. Ozone gas was passed through a mixture of methyl 4-(5-fluoro-2-methoxypyridin-4-yl)-3-(1-formylcyclopentyl)benzoate (0.13g, 0.36 mmol) in DCM (6.0 mL) and MeOH (1.5 mL) at -78°C for 10 minutes. The excess of ozone was purged off by nitrogen, and dimethylsulfide (0.3 mL) was added. The resulting reaction mixture was stirred at room temperature for 30 minutes. Sodium borohydride (0.13 mL, 3.6 mmol) was added, and the mixture was stirred at room temperature for 16 hours. The LCMS results indicated the reaction was completed. EtOAc (50 mL) was added, and the mixture was washed with brine (20 x 2 mL) and dried over Na₂SO₄. The solvent was removed, and the product thus obtained was good enough for use in the next step without further purification. MS ESI (pos.) m/e: 360.2 (M+H)⁺.



[01163] Methyl 4-(5-fluoro-2-methoxypyridin-4-yl)-3-(1-(methoxymethyl)cyclopentyl)benzoate (77.12B). To a suspension of sodium hydride (20.0 mg 60% in oil, 522 μmol) in DMF (1.0 mL) was slowly added 77.12A (75.0mg, 209.0 μmol) at 0°C. The resulting mixture was stirred at room temperature for 30 minutes. Methyl iodide (296.0 mg, 2087 μmol) was then added, and the reaction was stirred for 16 hours at room temperature. EtOAc (60.0 mL) was added, and the mixture was washed with brine (20 x 2 mL) and dried over MgSO_4 . The solvent was removed. The product was used in the next step without further purification. MS ESI (pos.) m/e: 374.0 (M+H)⁺.

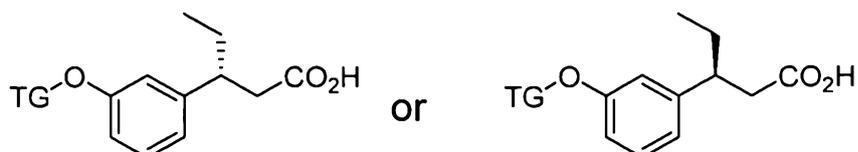


[01164] 4-(4-(Chloromethyl)-2-(1-(methoxymethyl)cyclopentyl)phenyl)-5-fluoro-2-methoxypyridine (77.12C). The reduction and chlorination of 77.12B to form 77.12C using the procedure described in Example 66.6. MS ESI (pos.) m/e: 364.2 (M+H)⁺.

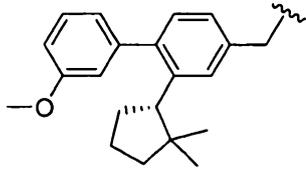
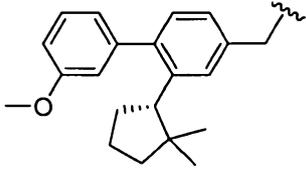
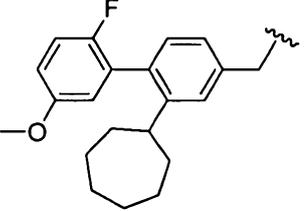
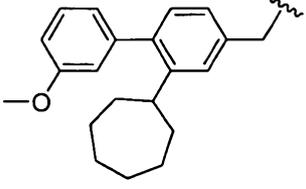
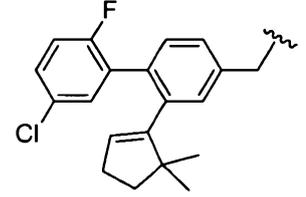
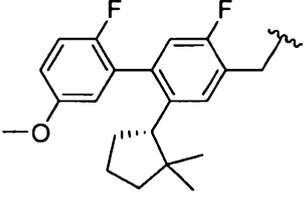
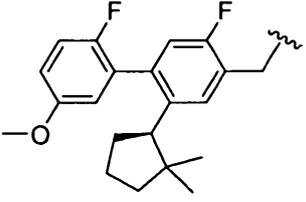
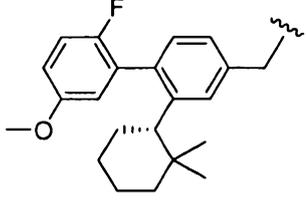
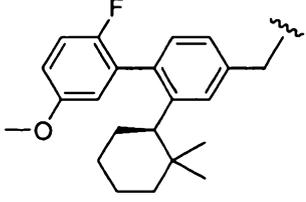
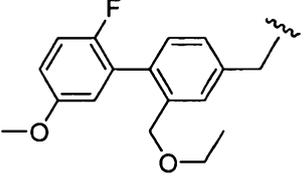
[01165] (3R)-3-(3-(4-(5-Fluoro-2-methoxypyridin-4-yl)-3-(1-(methoxymethyl)cyclopentyl)benzyloxy)-2-fluorophenyl)pentanoic acid or (3S)-3-(3-(4-(5-fluoro-2-methoxypyridin-4-yl)-3-(1-(methoxymethyl)cyclopentyl)benzyloxy)-2-fluorophenyl)pentanoic acid (77.12). Alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 using 77.12C and 77.G derived from peak one from the chiral separation of the racemic ester 77.F, described herein to yield 77.12. ¹H NMR (400 MHz, CDCl_3) δ ppm 7.94 (1 H, s), 7.44 (1 H, s), 6.92 (2 H, t, J=7.4 Hz), 6.84 (2 H, t, J=7.0 Hz), 6.56 - 6.79 (2 H, m), 5.09 (2 H, s), 3.88 (3 H, s), 3.25 - 3.36 (1 H, m), 3.16 - 3.25 (1 H, m), 3.16 (3 H, s), 2.65 (2 H, d, J=7.4 Hz), 1.80 - 1.96 (1 H, m), 1.46 - 1.76 (10 H, m), 0.68 - 0.85 (3 H, m). MS ESI (pos.) m/e: 540.3 (M+H)⁺.

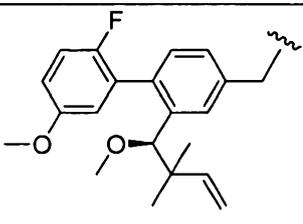
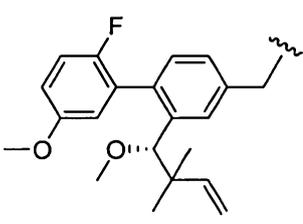
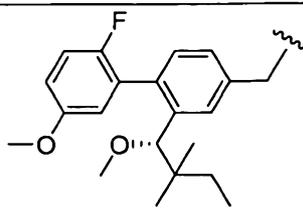
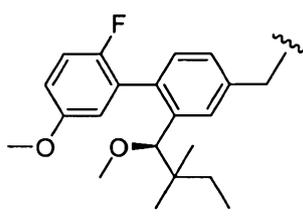
[01166] Example 78

[01167] Examples 78.1 and 78.2 are prepared and each of the other following compounds were prepared from 17.1 and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Examples 78.1 and 78.2 are prepared and each of the other compounds in the following table were prepared using the same enantiomer of the phenol.

Table 14

Compound	TG	Compound	TG
78.1		78.2	
78.3	 or 	78.4	 or but not the same one as 78.3
78.5	 or 	78.6	 or

Compound	TG	Compound	TG
			 but not the same one as 78.5
78.7		78.8	
78.9		78.10	 or 
78.11	 or 	78.12	

Compound	TG	Compound	TG
78.13	 or 	78.14	 or 

[01168] (3R)-3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid (78.1). This compound is prepared from 17.1 and the appropriate halomethyl or hydroxymethyl compound.

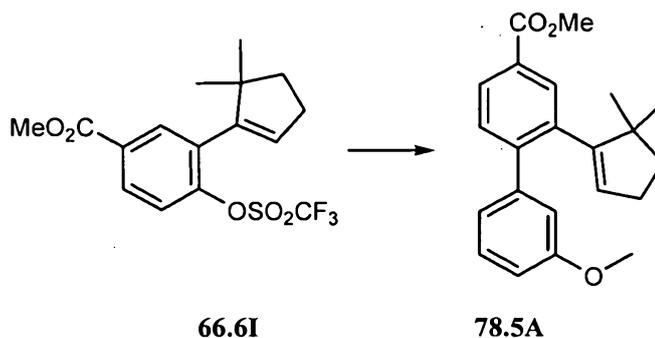
[01169] (3R)-3-(3-(((2-(2,2-Dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-(2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid (78.2). This compound is prepared from 17.1 and the appropriate halomethyl or hydroxymethyl compound.

[01170] (3R)-3-(3-(((2-((1R)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3R)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid (78.3). MS ESI (pos.) m/e: 522.2 (M+H₂O)⁺.

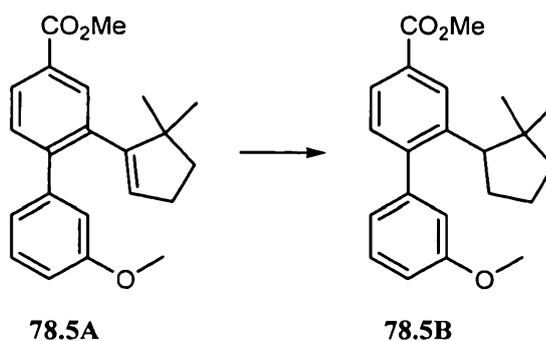
[01171] (3R)-3-(3-(((2-((1S)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-

yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid (78.4). MS ESI (pos.) m/e: 522.2 (M+H₂O)⁺, 527.2 (M+Na)⁺.

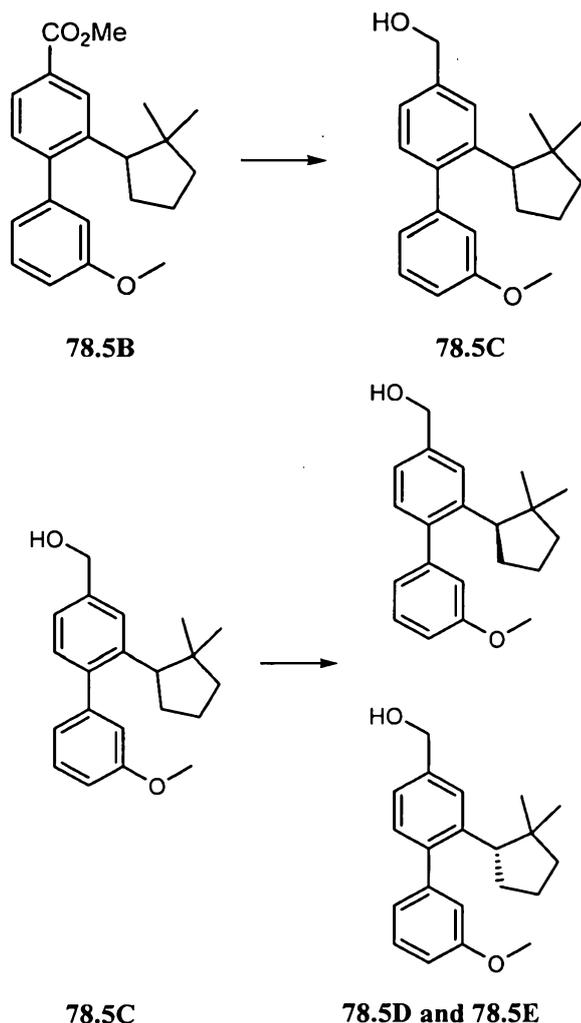
[01172] **Example 78.5**



[01173] **Methyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-3'-(methyloxy)-1,1'-biphenyl-4-carboxylate (78.5A).** To a stirred solution of **66.6I** (1.00 g, 2.6 mmol) in DMF (15.00 mL) at 23°C was added 3-methoxyphenylboronic acid (0.80 g, 5.3 mmol)(commercially available from Aldrich), potassium carbonate (1.1 g, 7.9 mmol), and then tetrakis(triphenylphosphine)palladium (0.31 g, 0.26 mmol). The mixture was heated to 90°C and stirred for 18 hours. The reaction was then cooled to room temperature, diluted with brine, and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure. The resulting product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **78.5A** as a colorless oil (0.80 g, 90% yield).

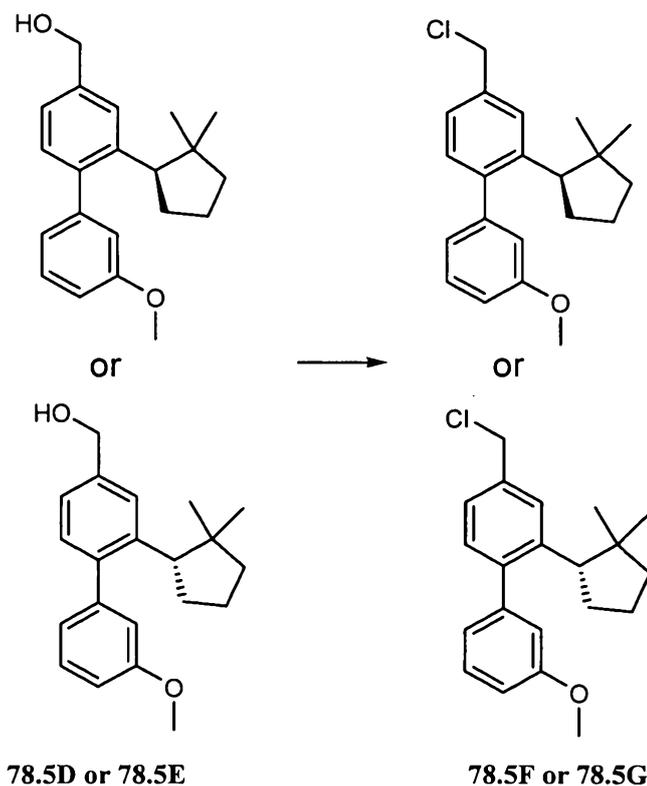


[01174] **Methyl 2-(2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-carboxylate (78.5B)**. To a stirred solution of **78.5A** (0.50 g, 1.5 mmol) in EtOAc (2.00 mL) at 23°C was added palladium on carbon (0.16 g, 1.5 mmol). The reaction was placed under an atmosphere of hydrogen and stirred for 19 hours. The reaction mixture was then filtered and the filtrate was concentrated in vacuo. The product was purified on silica gel (0-10% EtOAc in hexanes) to yield **78.5B** as a colorless oil (0.50 g, 99% yield).



[01175] **(2-((1R)-2,2-Dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methanol and (2-((1S)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methanol (78.5D and 78.5E)**. To a cooled solution of **78.5B** (0.500 g, 1.5 mmol) in dry THF (5.00 mL) at 0°C was added LAH (3.0 mL, 3.0 mmol, 1.0M) dropwise. Upon complete addition, the reaction was maintained at 0°C for 1.5 hours. 1N NaOH was then

added to quench the reaction, and the resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the product was purified on silica gel (0-20% EtOAc in hexanes) to yield **78.5C** as a colorless oil (0.25 g, 55% yield). Chiral separation of **78.5C** was accomplished on Chiracel-OD (3%IPA in hexane) to provide **78.5D** (peak one) and **78.5E** (peak two). Both enantiomers were used to synthesize example compounds, and both enantiomers gave active example compounds. However, the enantiomer corresponding to peak 2 provided the most active example compounds. MS ESI (pos.) m/e: 293.2 (M-OH)⁺.

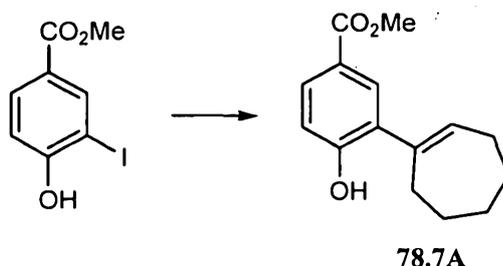


[01176] **4-(Chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl (78.F or 78.5G)**. To a stirred solution of **78.5D or 78.5E** (0.116 g, 0.4 mmol) in DCM (4 mL) and DMF (0.03 mL) at 0°C was added thionyl chloride (0.05 mL, 0.7 mmol). The reaction was then stirred at room temperature for one hour. The reaction mixture was concentrated in vacuo, and the product was purified on silica gel (0-20% EtOAc in hexanes) to yield **78.5F or 78.5G** as a colorless oil (0.100 g, 81% yield).

[01177] (3R)-3-(3-(((2-((1R)-2,2-Dimethylcyclopentyl)-3'-(methoxy))-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3R)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-3'-(methoxy))-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-3'-(methoxy))-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-3'-(methoxy))-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid (78.5). The title compound was prepared from chloromethyl compound 78.5F or 78.5G derived from 78.5E (peak two from the separation of the racemic alcohol) using the methods described herein. MS ESI (pos.) m/e: 504.2 (M+H₂O)⁺, 509.2 (M+Na)⁺.

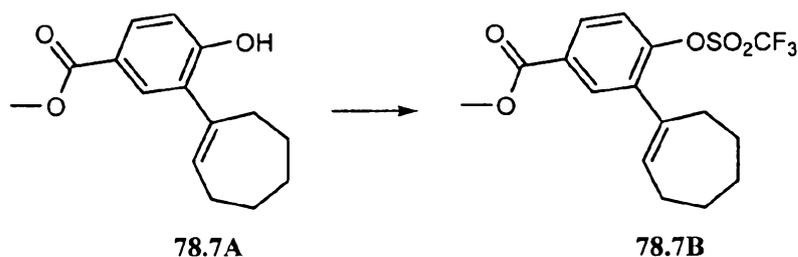
[01178] (3R)-3-(3-(((2-((1S)-2,2-Dimethylcyclopentyl)-3'-(methoxy))-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-3'-(methoxy))-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-3'-(methoxy))-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-3'-(methoxy))-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid (78.6). The title compound was prepared from chloromethyl compound 78.5F or 78.5G derived from 78.5D (peak one from the separation of the racemic alcohol) using the methods described herein. MS ESI (pos.) m/e: 504.2 (M+H₂O)⁺, 509.2 (M+Na)⁺.

[01179] **Example 78.7**

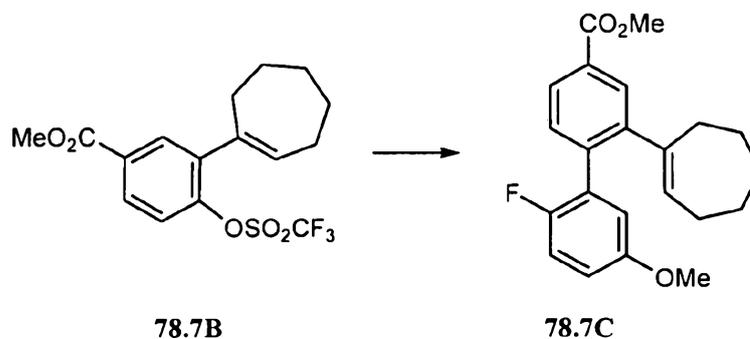


[01180] **Methyl 3-(1-cyclohepten-1-yl)-4-hydroxybenzoate (78.7A).** To a stirred solution of methyl 4-hydroxy-3-iodobenzoate (1.4 g, 5.0 mmol) (commercially available from Aldrich) in DMF (15 mL) at 23°C was added (Z)-cycloheptenylboronic acid (0.74 g, 5.3 mmol, commercially available from Combi-Blocks), potassium

carbonate (2.1 g, 15 mmol), followed by tetrakis(triphenylphosphine)palladium (0.58 g, 0.50 mmol). The mixture was heated to 100°C. The reaction was then stirred for 17 hours and then cooled to room temperature. The reaction was diluted with brine and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **78.7A** as a colorless oil (0.55 g, 44% yield).

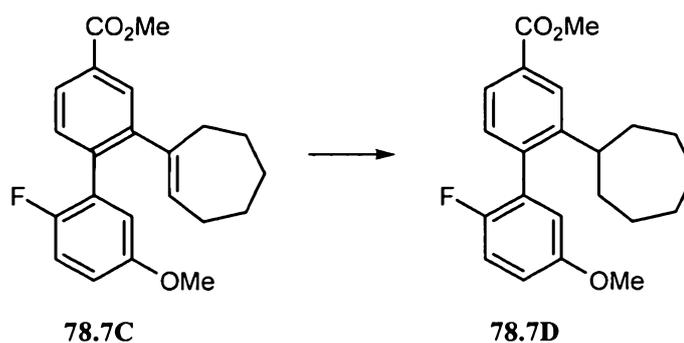


[01181] Methyl 3-(1-cyclohepten-1-yl)-4-(((trifluoromethyl)sulfonyl)oxy)benzoate (78.7B). To a stirred solution of methyl 3-(1-cyclohepten-1-yl)-4-hydroxybenzoate **78.7A** (0.550 g, 2.23 mmol) in DCM (10.00 mL) at 0°C was added TEA (0.373 mL, 2.68 mmol), and DMAP (catalytic). N-phenyltriflimide (0.878 g, 2.46 mmol), was then added and the reaction mixture was stirred at room temperature for 22 hours. The reaction was then diluted with brine and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-5% EtOAc in hexanes) to yield **78.7B** as a colorless oil (0.700 g, 83% yield).

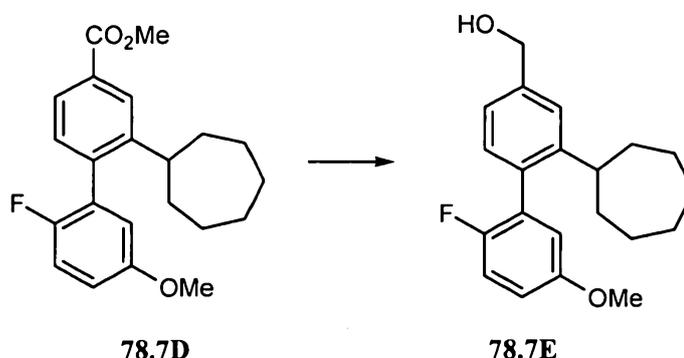


[01182] Methyl 2-(1-cyclohepten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (78.7C). To a stirred solution of **78.7B** (0.350 g, 0.93 mmol) in DMF (5.00 mL) at 23°C was added 2-fluoro-5-methoxyphenylboronic acid (0.31 g, 1.9

mmol)(commercially available from Aldrich), potassium carbonate (0.38 g, 2.8 mmol), and then tetrakis(triphenylphosphine)palladium (0.11 g, 0.093 mmol). The mixture was heated to 90°C and stirred for 19 hours. The reaction was then cooled to room temperature, diluted with brine, and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure. The product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **78.7C** as a colorless oil (0.262 g, 80% yield).



[01183] **Methyl 2-cycloheptyl-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (78.7D)**. To a stirred solution of **78.7C** (0.262 g, 0.74 mmol) in EtOAc (2.00 mL) at 23°C was added palladium on carbon (0.079 g, 0.74 mmol). The reaction mixture was placed under an atmosphere of hydrogen and stirred for 3 hours. The reaction mixture was then filtered and concentrated in vacuo to yield **78.7D** as a colorless oil (0.260 g, 99% yield).

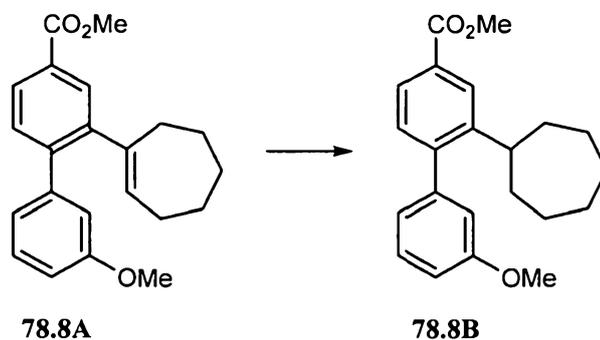


[01184] **(2-Cycloheptyl-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (78.7E)**. To a stirred solution of **78.7D** (0.260 g, 0.7 mmol) in THF (7 mL) at 0°C was added LAH (1 mL, 1 mmol, 1.0M). The reaction was stirred for one hour and then 1N

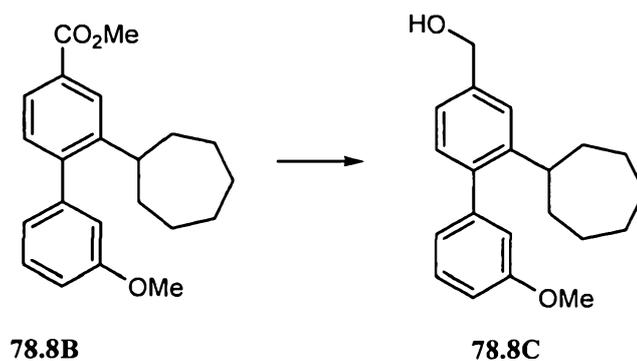
78.7B

78.8A

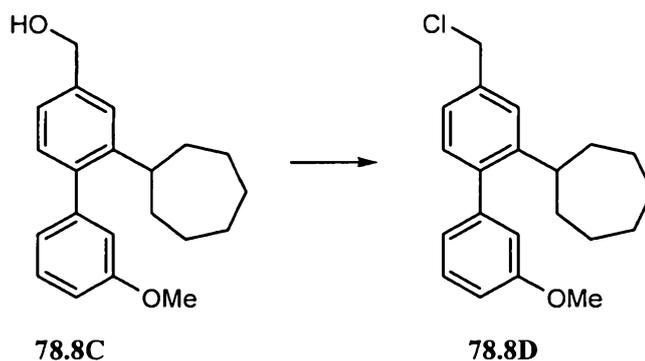
[01188] **Methyl 2-(1-cyclohepten-1-yl)-3'-(methoxy)-1,1'-biphenyl-4-carboxylate (78.8A)**. To a stirred solution of **78.8B** (0.350 g, 0.93 mmol) in DMF (5.00 mL) at 23°C was added 3-methoxyphenylboronic acid (0.28 g, 1.9 mmol) (commercially available from Aldrich), potassium carbonate (0.38 g, 2.8 mmol), and then tetrakis(triphenylphosphine)palladium (0.11 g, 0.093 mmol). The mixture was heated to 90°C and stirred for 18 hours and then cooled to room temperature. The reaction was diluted with brine and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **78.8A** as a colorless oil (0.291 g, 94% yield).



[01189] **Methyl 2-cycloheptyl-3'-(methoxy)-1,1'-biphenyl-4-carboxylate (78.8B)**. To a stirred solution of **78.8A** (0.291 g, 0.86 mmol) in EtOAc (2.00 mL) at 23°C was added palladium on carbon (0.092 g, 0.86 mmol). The reaction was placed under an atmosphere of hydrogen and stirred for four hours. The reaction was then concentrated in vacuo to yield **78.8B** (0.290 g, 99% yield).



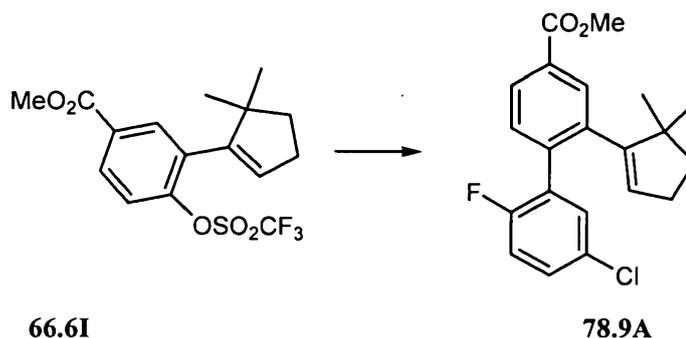
[01190] (2-Cycloheptyl-3'-(methoxy)-1,1'-biphenyl-4-yl)methanol (78.8C).
 To a stirred solution of **78.8B** (0.290 g, 0.86 mmol) in THF (8.6 mL, 0.86 mmol) at 0°C was added LAH (1.7 mL, 1.7 mmol, 1.0M). The reaction was stirred for one hour and then 1N NaOH was added to quench the reaction. The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **78.7C** as a colorless oil (0.220 g, 83% yield). MS ESI (pos.) m/e: 293.2 (M-OH)⁺.



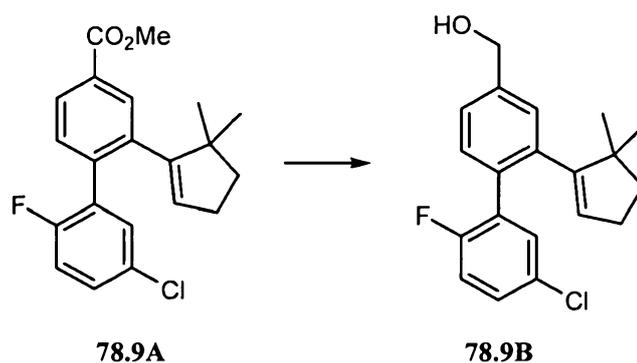
[01191] 4-(Chloromethyl)-2-cycloheptyl-3'-(methoxy)-1,1'-biphenyl (78.8D).
 To a stirred solution of **78.8C** (0.212 g, 0.7 mmol) in DCM (7 mL) and DMF (0.05 mL) at 0°C was added thionyl chloride (0.10 mL, 1 mmol). The reaction was stirred for one hour and then concentrated in vacuo. The product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **78.7D** as a colorless oil (0.185 g, 82% yield)

[01192] (3R)-3-(3-(((2-Cycloheptyl-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-cycloheptyl-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid (78.8). The title compound was prepared from **78.D** using the methods described herein. MS ESI (pos.) m/e: 504.2 (M+H₂O)⁺, 509.2 (M+Na)⁺.

[01193] Example 78.9

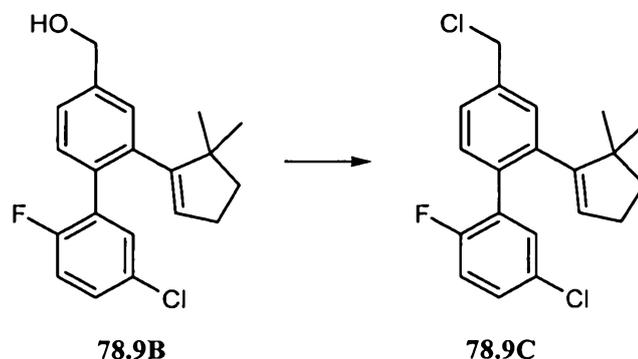


[01194] **Methyl 5'-chloro-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-carboxylate (78.9A).** To a stirred solution of methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-(trifluoromethylsulfonyloxy)benzoate **66.6I** (0.100 g, 0.3 mmol) in DMF (4 mL) at 23°C was added 5-chloro-2-fluorophenylboronic acid (0.07 g, 0.4 mmol) (commercially available from Aldrich), potassium carbonate (0.1 g, 0.8 mmol), followed by tetrakis(triphenylphosphine)palladium (0.03 g, 0.03 mmol). The mixture was heated to 90°C and stirring was continued for 23 hours. The reaction was then cooled to room temperature. The reaction was diluted with brine and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was purified on silica gel (0-10% EtOAc in hexanes) to yield **78.9A** as a colorless oil (0.082 g, 86% yield).

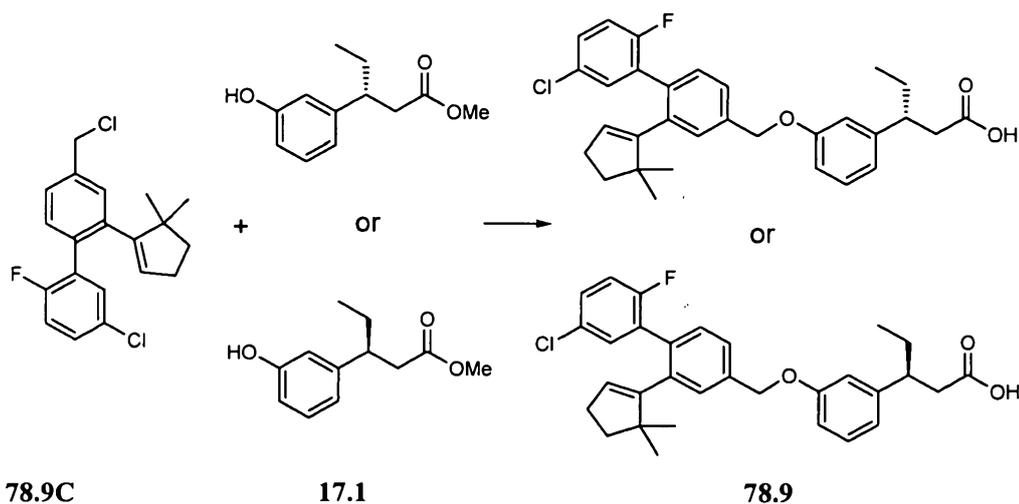


[01195] **(5'-Chloro-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-yl)methanol (78.9B).** To a stirred solution of **78.9A** (0.082 g, 0.23 mmol) in THF (5.00 mL) at 0°C was added LAH (0.46 mL, 0.46 mmol, 1.0M). The reaction was then stirred for 1.5 hours. 1N NaOH(aq) was then added to quench the reaction. The reaction was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the

product was purified on silica gel (0-20% EtOAc in hexanes) to yield **78.9B** as a colorless oil (0.048 g, 63% yield).



[01196] **5'-Chloro-4-(chloromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl (78.9C)**. To a stirred solution of **78.9B** (0.048 g, 0.1 mmol) in DCM (2.00 mL) at 23°C was added DMF (0.001 mL) followed by thionyl chloride (0.02 mL, 0.3 mmol). The reaction was stirred for one hour and then concentrated in vacuo. The product was purified on silica gel (0-10% EtOAc in hexanes) to yield **78.9C** as a colorless oil (0.05 g, 99% yield).



[01197] **(3R)-3-(3-(((5'-Chloro-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((5'-chloro-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid 78.9**. The alkylation and hydrolysis were

conducted in an analogous manner to Example 66.6 (described herein) to yield 78.9 (0.0391 g, 80% yield). MS ESI (neg.) m/e: 505.1 (M-H)⁺.

[01198] (3R)-3-(3-(((2-((1S)-2,2-Dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid (78.10). Example 78.10 was prepared using the alkylation and hydrolysis procedure of Example 66.6 using 17.1 and 66.44D derived from peak one from the chiral separation of the racemic alcohol 66.44A on the OJ column, described herein to yield 78.10. MS ESI (neg.) m/e: 520.9 (M-H)⁺.

[01199] (3R)-3-(3-(((2-((1S)-2,2-Dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid (78.11). MS ESI (neg.) m/e: 517.3 (M-H)⁺.

[01200] (3R)-3-(3-(((2-((Ethyloxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-((ethyloxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid (78.12). Example 78.12 was prepared using an alkylation and hydrolysis procedure similar to that in Example 67.23 using 17.1 and 67.23C and also using chloromethyl compound 78.5F or 78.5G derived from 78.5D (peak one from the separation of the racemic alcohol). MS ESI (neg.) m/e: 465 (M-H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 7.60 (m, 1H), 7.45 (m, 1H), 7.19-7.27 (m, 3H), 6.96 (m, 1H), 6.87 (m, 3H), 6.79 (m, 1H), 5.14 (s, 2H), 4.29 (s, 2H), 3.76 (s, 3H), 3.34 (m, 2H), 2.86 (m, 1H), 2.43-2.57 (m, 2H), 1.64 (m, 2H), 1.51 (m, 2H), 1.04 (t, 3H), 0.70 (t, 3H).

[01201] (3R)-3-(3-(((2-((1S)-2,2-Dimethyl-1-(methoxy)-3-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)-3-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-

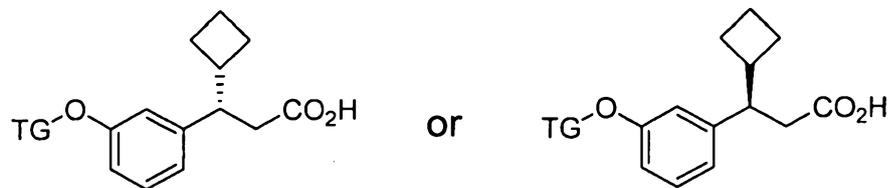
biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)-3-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)-3-butenyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid (78.13). Example 78.13 was prepared using an alkylation and hydrolysis procedure analogous to that used for Example 66.6 (using 17.1, also using 66.24C (derived from peak two from the chiral separation of the reduction product of 67.24A), described herein). MS ESI (neg.) m/e: 519 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.54-7.58 (m, 1H), 7.43-7.45 (m, 1H), 7.22-7.25 (m, 2H), 7.20 (m, 1H), 6.80-6.85 (m, 4H), 6.73-6.75 (m, 1H), 5.75 (m, 1H), 5.14 (m, 2H), 4.71-4.86 (m, 2H), 4.22 (m, 1H), 3.81 (m, 2H), 3.29 (m, 3H), 2.98 (m, 1H), 2.64 (m, 2H), 1.61-1.73 (m, 2H), 1.29 (m, 3H), 0.76-0.84 (m, 9H).

[01202] (3R)-3-(3-(((2-((1S)-2,2-Dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)butyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid (78.14). Example 78.14 was prepared using an alkylation and hydrolysis procedure analogous to that of Example 66.62 (using 17.1 and using 66.62E (derived from peak one from the chiral separation of the reduction and alkylation product of 66.62B), described herein)MS ESI (neg.) m/e: 521 (M-H)⁺. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.57 (m, 1H), 7.43 (m, 1H), 7.20 (m, 2H), 7.02 (m, 1H), 6.80-6.87 (m, 4H), 6.75 (m, 1H), 5.16 (m, 2H), 4.05-4.29 (m, 1H), 3.80 (s, 3H), 3.23-3.28 (m, 3H), 2.98 (m, 1H), 2.64 (m, 2H), 1.71 (m, 1H), 1.63 (m, 1H), 1.27 (m, 3H), 1.18 (m, 1H), 0.81 (m, 3H), 0.71 (s, 3H), 0.60 (t, 3H), 0.49-0.51 (m, 3H)

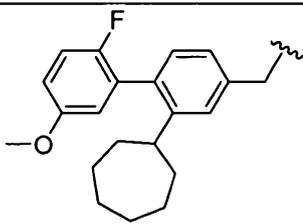
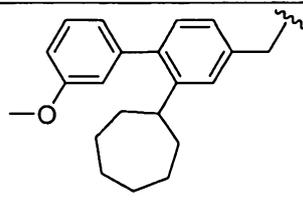
[01203] **Example 79**

[01204] Examples 79.1 and 79.2 are prepared and each of the other following compounds were prepared from 70 and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Examples 79.1 and 79.2 are prepared and each of the other compounds in the following table were prepared using the same enantiomer of the phenol.

Table 15



Compound	TG	Compound	TG
79.1		79.2	
79.3	 or 	79.4	 or but not the same one as 79.3
79.5	 or 	79.6	 or but not the same one as 79.5

Compound	TG	Compound	TG
79.7		79.8	

[01205] (3S)-3-Cyclobutyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclobutyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (79.1). This compound is prepared from 70 and the appropriate halomethyl or hydroxymethyl compound.

[01206] (3S)-3-Cyclobutyl-3-(3-(((2-(2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclobutyl-3-(3-(((2-(2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (79.2). This compound is prepared from 70 and the appropriate halomethyl or hydroxymethyl compound.

[01207] (3S)-3-Cyclobutyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclobutyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclobutyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclobutyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (79.3). MS ESI (pos.) m/e: 548.3 (M+H₂O)⁺, 553.3 (M+Na)⁺.

[01208] (3S)-3-Cyclobutyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclobutyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclobutyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclobutyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-

yl)methyl)oxy)phenyl)propanoic acid (79.4). MS ESI (pos.) m/e: 548.3 (M+H₂O)⁺, 553.3 (M+Na)⁺.

[01209] (3S)-3-Cyclobutyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclobutyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclobutyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclobutyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (79.5). MS ESI (pos.) m/e: 530.3 (M+H₂O)⁺, 535.3 (M+Na)⁺.

[01210] (3S)-3-Cyclobutyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclobutyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclobutyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclobutyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (79.6). MS ESI (pos.) m/e: 530.3 (M+H₂O)⁺, 535.3 (M+Na)⁺.

[01211] (3S)-3-(3-(((2-Cycloheptyl-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclobutylpropanoic acid or (3R)-3-(3-(((2-cycloheptyl-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclobutylpropanoic acid (79.7). MS ESI (pos.) m/e: 548.3 (M+H₂O)⁺, 553.3 (M+Na)⁺.

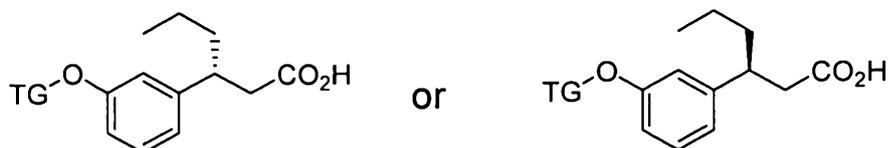
[01212] (3S)-3-(3-(((2-Cycloheptyl-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclobutylpropanoic acid or (3R)-3-(3-(((2-cycloheptyl-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-cyclobutylpropanoic acid (79.8). MS ESI (pos.) m/e: 530.3 (M+H₂O)⁺, 535.3 (M+Na)⁺.

[01213] **Example 80**

[01214] Example 80.2 is prepared and each of the other following compounds were prepared from 43.6 and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Example 80.2 is prepared and each of the

other compounds in the following table were prepared using the same enantiomer of the phenol.

Table 16



Compound	TG	Compound	TG
80.1		80.2	
80.3	 or 	80.4	 or but not the same one as 80.3
80.5	 or 	80.6	 or

Compound	TG	Compound	TG
			but not the same one as 80.5

[01215] (3R)-3-(3-(((2-Cycloheptyl-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-cycloheptyl-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (80.1). MS ESI (pos.) m/e: 518.3 (M+H₂O)⁺, 523.3 (M+Na)⁺.

[01216] (3R)-3-(3-(((2-(2,2-Dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-(2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (80.2). This compound is prepared from 43.6 and the appropriate halomethyl or hydroxymethyl compound.

[01217] (3R)-3-(3-(((2-((1R)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3R)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (80.3). MS ESI (pos.) m/e: 536.3 (M+H₂O)⁺, 541.3 (M+Na)⁺.

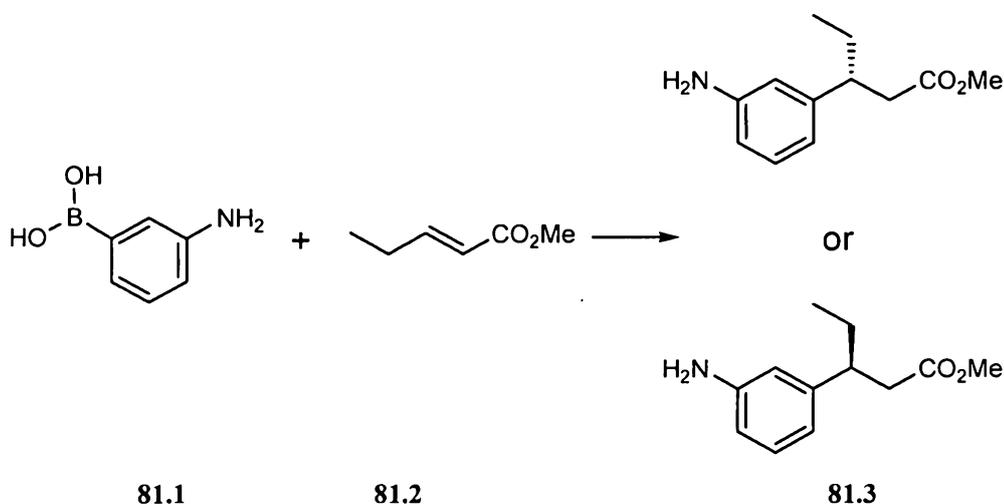
[01218] (3R)-3-(3-(((2-((1S)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (80.4). MS ESI (pos.) m/e: 536.3 (M+H₂O)⁺, 541.3 (M+Na)⁺.

[01219] (3R)-3-(3-(((2-((1R)-2,2-Dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3R)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-

yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (80.5). MS ESI (pos.) m/e: 518.3 (M+H₂O)⁺, 523.3 (M+Na)⁺.

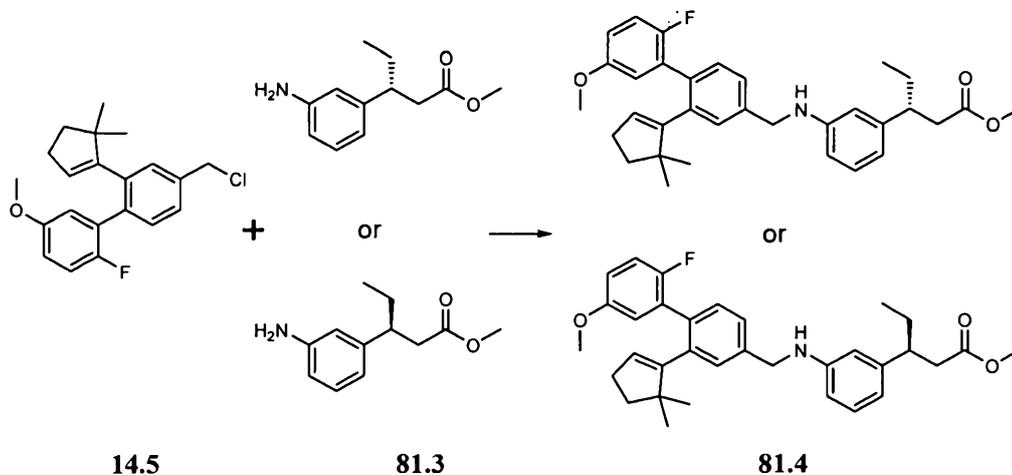
[01220] (3R)-3-(3-(((2-((1S)-2,2-Dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-3'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)hexanoic acid (80.6). MS ESI (pos.) m/e: 518.3 (M+H₂O)⁺, 523.3 (M+Na)⁺.

[01221] **Example 81**

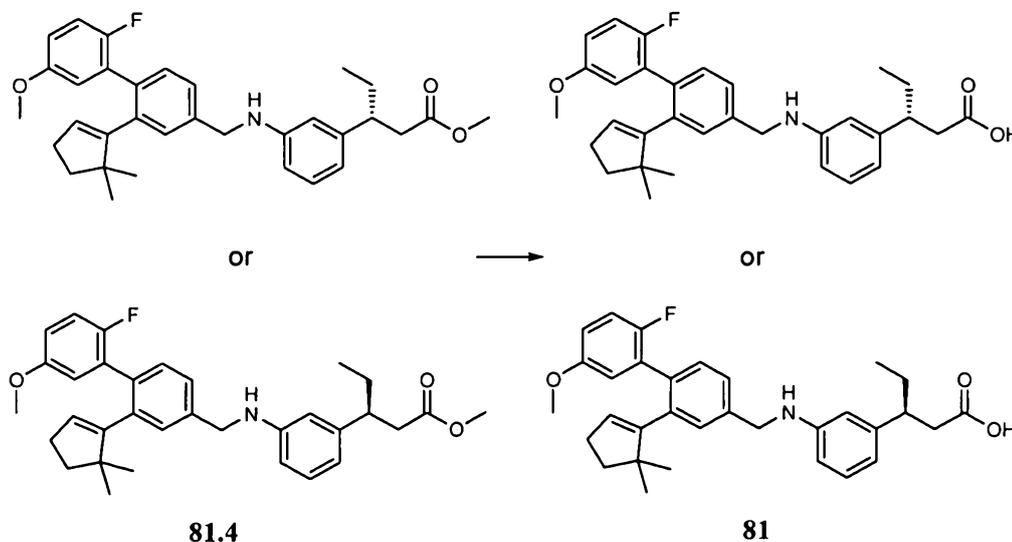


[01222] (R)-Methyl 3-(3-aminophenyl)pentanoate or (S)-methyl 3-(3-aminophenyl)pentanoate (81.3). A mixture of dioxane and water (10/1 dioxane/water, 22 mL) was added to a flask charged with hydroxyl[(S)-Binap]-rhodium(I) dimer (260 mg, 175 μ mol), and 3-aminophenylboronic acid hydrate (81.1)(available from Aldrich)(3.394 g, 21902 μ mol) and flushed with nitrogen and (E)-methyl pent-2-enoate (81.2)(available from Acros)(0.500 g, 4380 μ mol). The resulting mixture was then stirred at 40°C overnight. The reaction was diluted with EtOAc and washed with saturated sodium bicarbonate and brine, and then dried over sodium sulfate, filtered, and concentrated. The crude was purified by combiflash chromatography (0 to 20% EtOAc/Hexanes) to provide (R)-methyl 3-(3-aminophenyl)pentanoate or (S)-methyl 3-(3-

aminophenyl)pentanoate (**8.3**) (400 mg, 44.1% yield). The product is believed to be the R enantiomer.

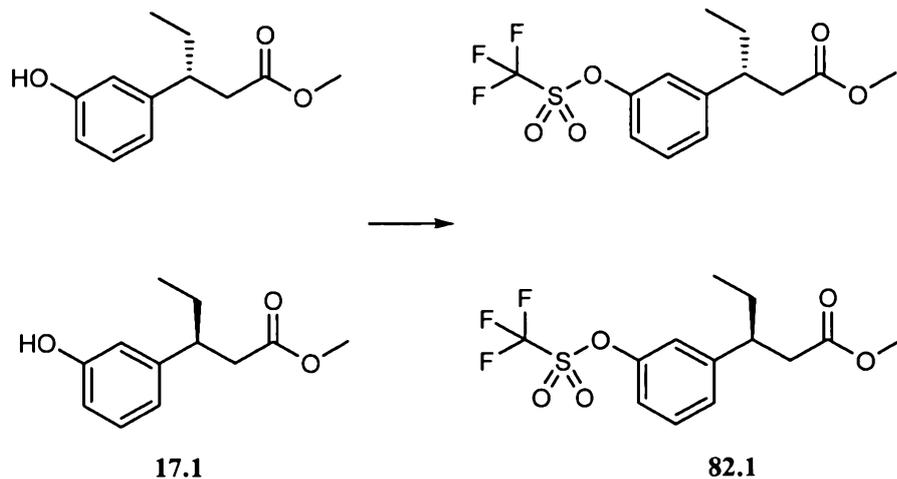


[01223] **Methyl (3R)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)amino)phenyl)pentanoate or methyl (3S)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)amino)phenyl)pentanoate (**81.4**)**. To a flask containing **81.3** (20.0 mg, 96 μ mol) and cesium carbonate (41 mg, 125 μ mol) in DMF (1 mL) was added **14.5** (33 mg, 96 μ mol), and the resulting mixture was stirred overnight. The reaction was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 , filtered, concentrated, and then purified by silica gel chromatography (0 to 20% EtOAc/Hexanes) to provide (**81.4**) (4.8 mg, 9.6% yield).



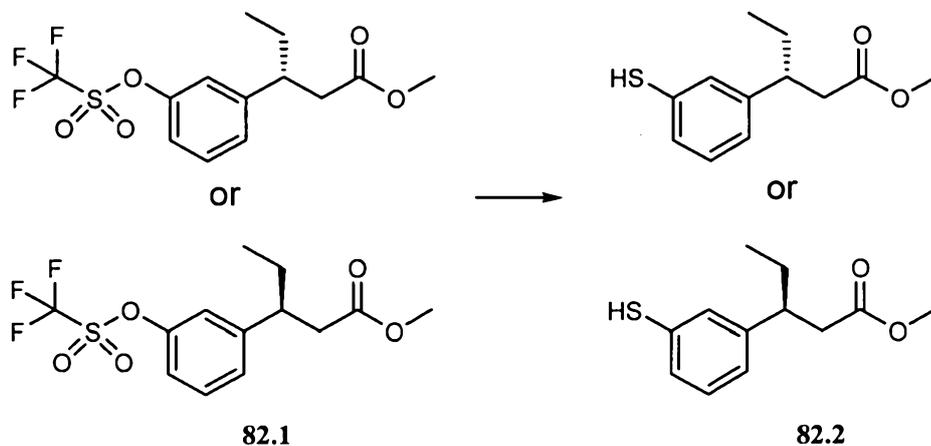
[01224] (3R)-3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)amino)phenyl)pentanoic acid or (3S)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)amino)phenyl)pentanoic acid (**81**). To a solution of **81.4** (5.0 mg, 9.7 μ mol) in THF/MeOH (2/1)(1.5 mL) was added LiOH (0.50 mL, 500 μ mol). The resulting mixture was stirred overnight at 23°C, quenched with excess 1N HCl, and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The crude residue was purified by combiflash chromatography (0 to 40% EtOAc/hexanes) to afford **81** (2.8 mg, 58% yield). MS ESI (neg.) m/e: 500.2 (M-H)⁻. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.28 - 7.34 (2 H, m), 7.24 (1 H, d, J=1.2 Hz), 7.13 (1 H, t, J=7.8 Hz), 6.94 - 6.98 (1 H, m), 6.77 - 6.80 (2 H, m), 6.57 (1 H, d, J=7.6 Hz), 6.54 (1 H, dd, J=8.1, 1.5 Hz), 6.50 (1 H, d, J=2.0 Hz), 5.50 (1 H, s), 4.36 (2 H, s), 3.76 (3 H, s), 2.91 (1 H, m), 2.62 (2 H, dd, J=7.3, 3.4 Hz), 2.24 (2 H, td, J=7.1, 2.4 Hz), 1.75-1.55 (5 H, m), 0.83 (6 H, s), 0.80 (3 H, t, J=7.3 Hz).

[01225] **Example 82**

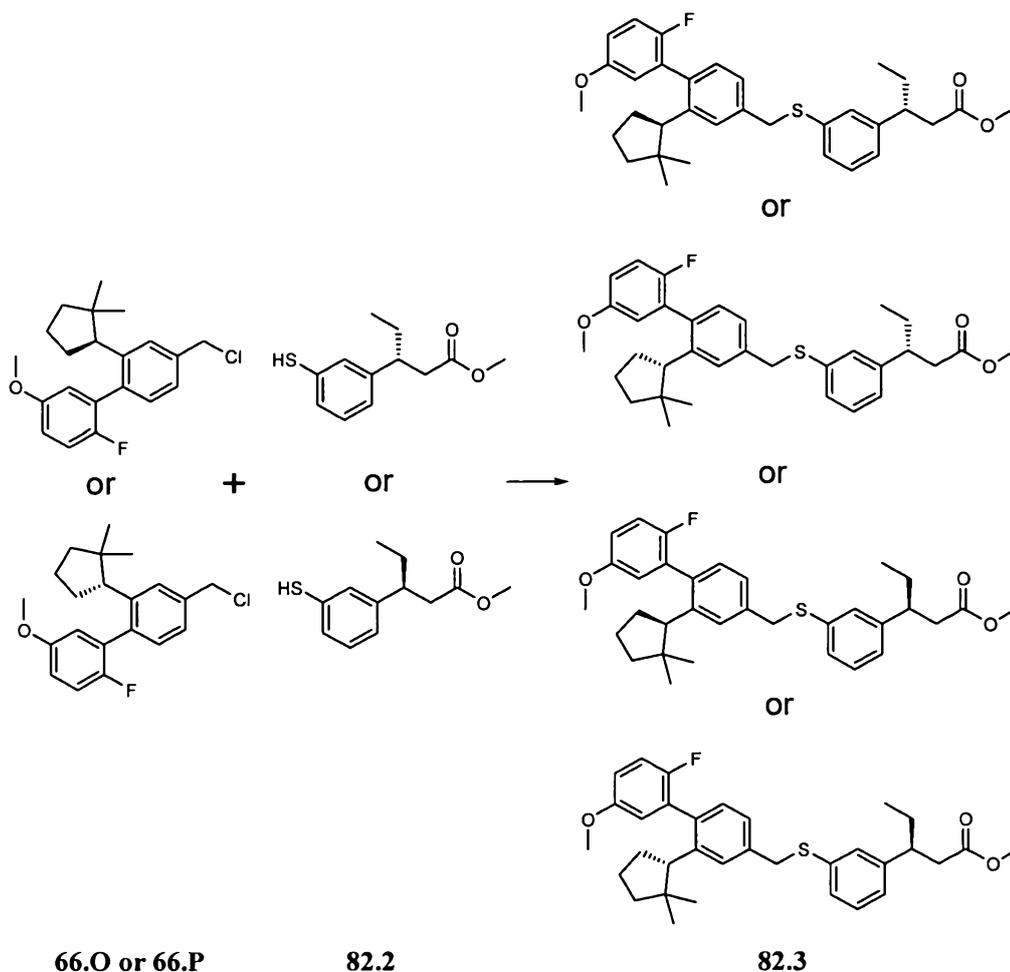


[01226] (R)-Methyl 3-(3-(trifluoromethylsulfonyloxy)-phenyl)pentanoate or (S)-methyl 3-(3-(trifluoromethylsulfonyloxy)-phenyl)pentanoate (**82.1**). To a stirred solution of **17.1** (280.0 mg, 1345 μ mol) in dry DCM (1 mL) was added N,N-dimethylpyridin-4-amine (16.43 mg, 134.5 μ mol) and TEA (374.0 μ L, 2689 μ mol). After about 20 minutes, N-phenyl-bis(trifluoromethanesulfonimide) (576.4 mg, 1613 μ mol) was added in portions. Upon complete addition, the solution was stirred at room temperature. After 3 hours, the reaction was diluted with brine and extracted three times with DCM. After drying over anhydrous magnesium sulfate and filtration, the organic

solvent was removed under reduced pressure and the residue was then purified with silica gel chromatography on a 12 g column using 0-15% EtOAc in hexanes to yield a colorless oil as (R)-methyl 3-(3-(trifluoromethylsulfonyloxy)phenyl)pentanoate or (S)-methyl 3-(3-(trifluoromethylsulfonyloxy)phenyl)pentanoate **82.1** (311.7 mg, 68.12% yield). The product is believed to be the R enantiomer.

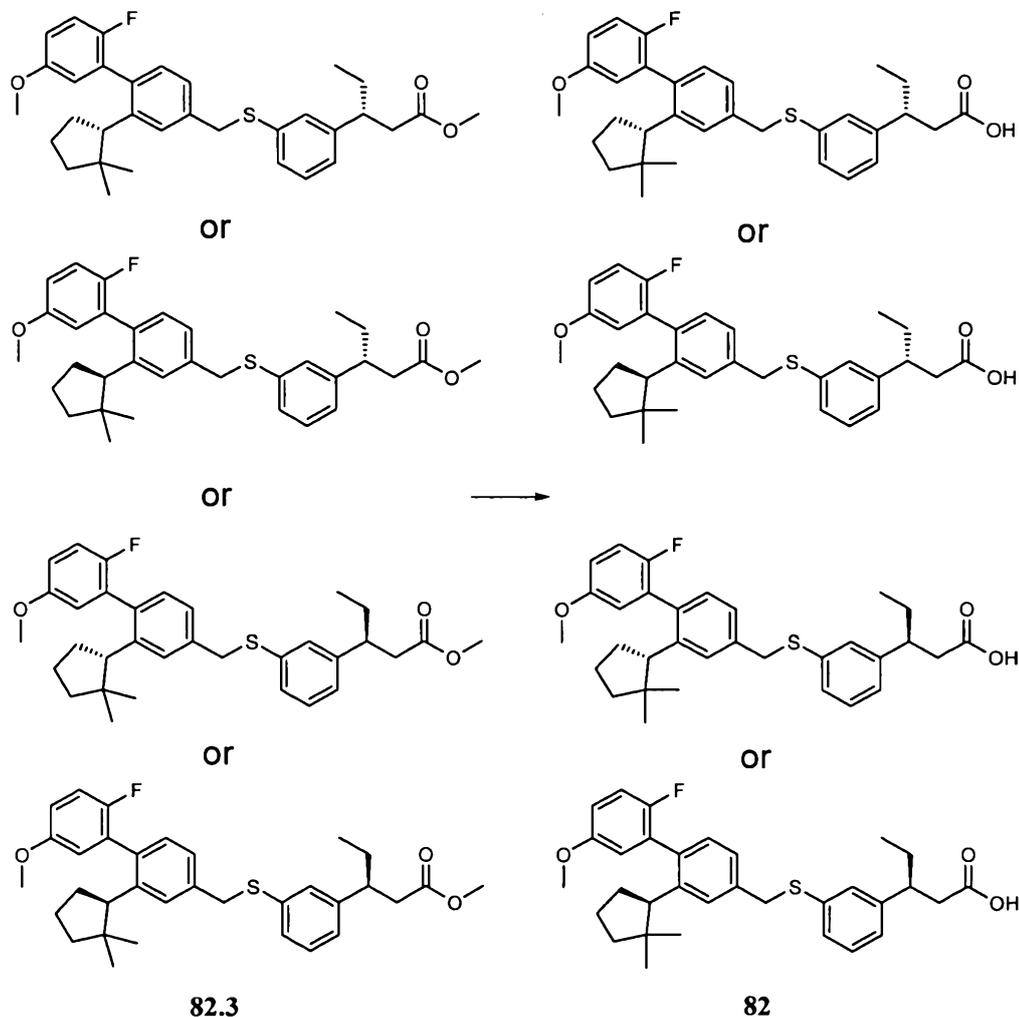


[01227] **(R)-Methyl 3-(3-(triisopropylsilylthio)phenyl)pentanoate or (S)-methyl 3-(3-(triisopropylsilylthio)phenyl)pentanoate (2.2)**. A vial was charged with Pd(PPh₃)₄ (13 mg, 11 μmol), cesium carbonate (92 mg, 283 μmol) and **82.1** (74 mg, 217 μmol). The vial was sealed, toluene (3 mL) was added, and the vial was sparged with nitrogen. Tips-thiol (61 μL, 283 μmol) was then added, and the reaction was heated at 100°C for 16 hours. After cooling to room temperature, tetrabutylammonium fluoride (294 μL, 294 μmol) was added, and the resulting mixture was stirred for two hours. The reaction was concentrated and purified using silica chromatography to provide **82.2** (42.2 mg, 51% yield).



[01228] Methyl (3R)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)sulfanyl)phenyl)pentanoate or methyl (3R)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)sulfanyl)phenyl)pentanoate or methyl (3S)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)sulfanyl)phenyl)pentanoate or methyl (3S)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)sulfanyl)phenyl)pentanoate (**82.3**). To a flask containing **82.2** (30.0 mg, 134 μ mol) and cesium carbonate (51.5 mg, 158 μ mol) in DMF (1 mL) was added 4-(chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl (**66.O** or **66.P**) (42.2 mg, 122 μ mol). The resulting mixture was then stirred overnight. The reaction was next diluted with water and extracted with EtOAc. The

combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, concentrated, and then purified by combiflash chromatography (0 to 20% EtOAc/Hexanes) to provide **82.3** (50.2 mg, 77.2% yield).

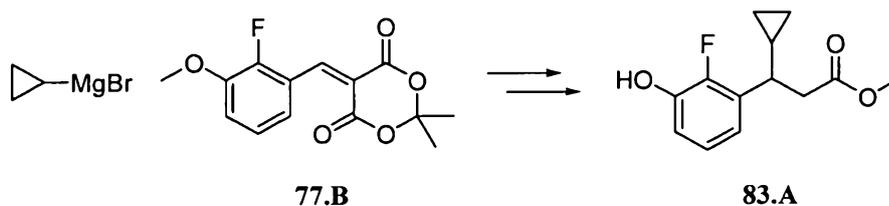


[01229] **(3R)-3-(3-(((2-((1S)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)sulfanyl)phenyl)pentanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)sulfanyl)phenyl)pentanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)sulfanyl)phenyl)pentanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)sulfanyl)phenyl)pentanoic acid (**82**). To a solution of **82.3** (10.0 mg, 19 μmol) in THF/MeOH (2/1) (1.5 mL) was added LiOH (0.500 mL, 500 μmol). The**

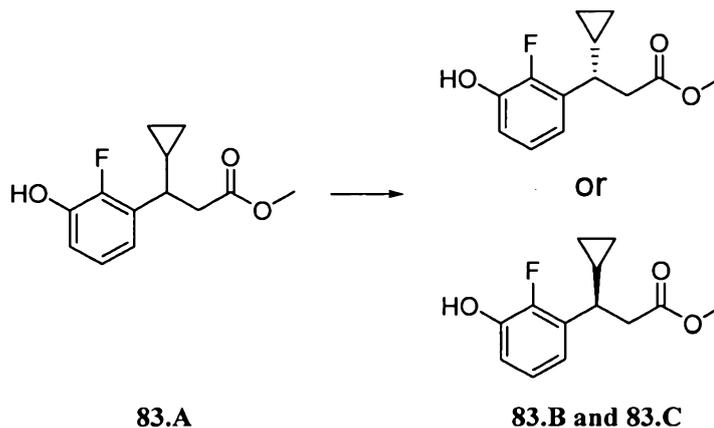
resulting mixture was stirred overnight at 23°C, quenched with excess 1N HCl, and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The residue was purified by combiflash chromatography (0 to 40% EtOAc/hexanes) to afford **82** (6.9 mg, 71% yield). MS ESI (neg.) m/e: 519.2 (M-H)⁺.

[01230] **Example 83**

[01231] **Synthesis of (S)-methyl 3-cyclopropyl-3-(2-fluoro-3-hydroxyphenyl)propanoate and (R)-methyl 3-cyclopropyl-3-(2-fluoro-3-hydroxyphenyl)propanoate (83.B and 83.C).**



[01232] **Methyl 3-cyclopropyl-3-(2-fluoro-3-hydroxyphenyl)propanoate (83.A).** Compound **83.A** was prepared from **77.B** and cyclopropylmagnesium bromide (0.5 M in THF)(commercially available from Aldrich) according to the analogous methods described in Example 77.

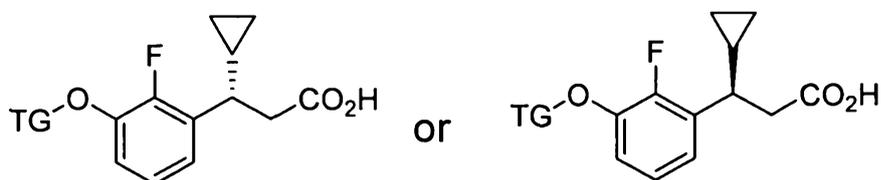


[01233] **(S)-Methyl 3-cyclopropyl-3-(2-fluoro-3-hydroxyphenyl)propanoate and (R)-methyl 3-cyclopropyl-3-(2-fluoro-3-hydroxyphenyl)propanoate (83.B and 83.C).** Racemic **83.A** (20 g, 84 mmol) was resolved by chiral HPLC (Chiralcel OD column, 3% IPA/hexane, detection at 220 nm) to afford (in order of elution) **83.B** (8.8 g, 88% yield, 99% e.e.) and **83.C** (8.8 g, 88% yield, 99% e.e.) as white needles. **83.B** is believed to be the S enantiomer.

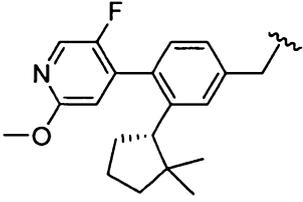
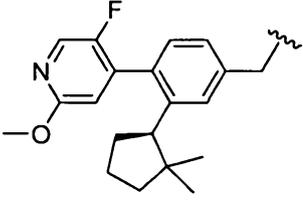
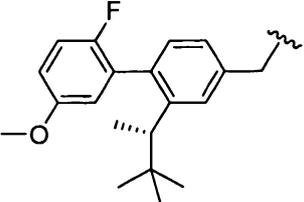
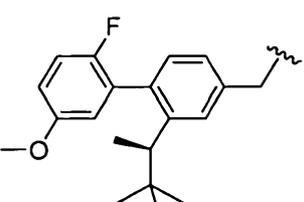
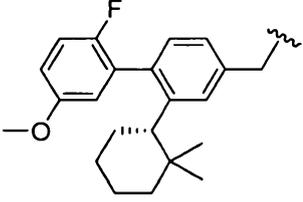
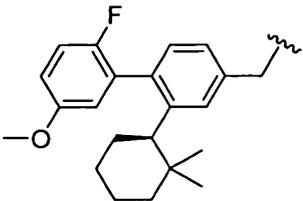
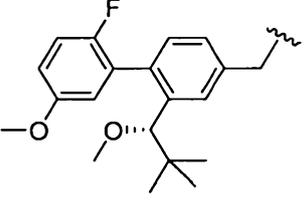
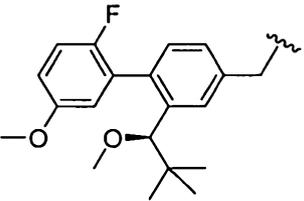
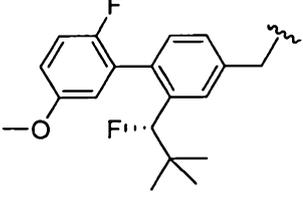
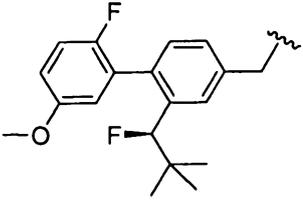
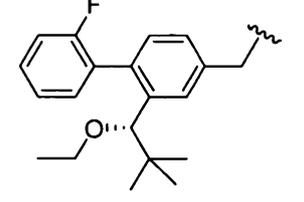
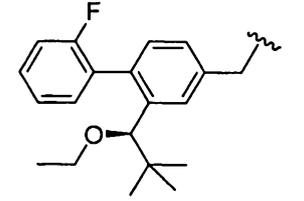
[01234] The following compounds were prepared from **83.B** and the appropriate

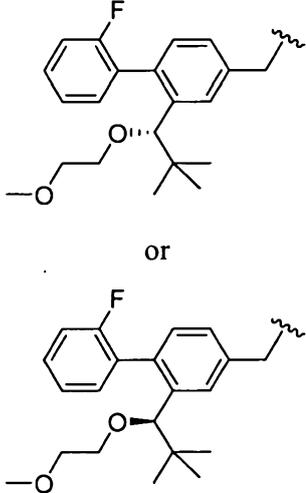
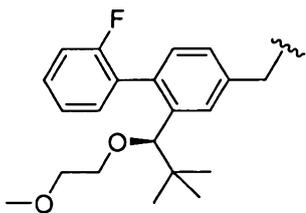
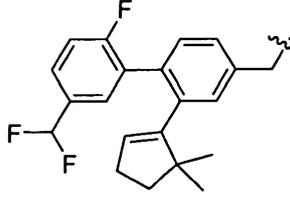
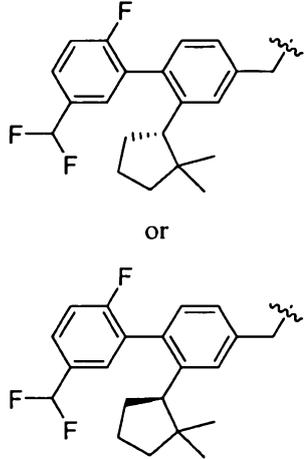
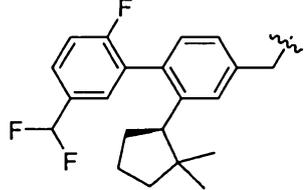
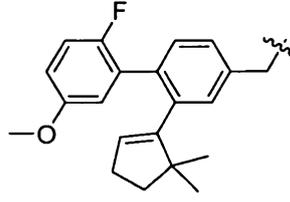
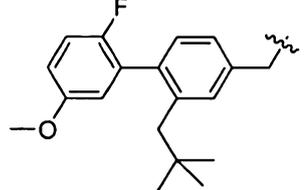
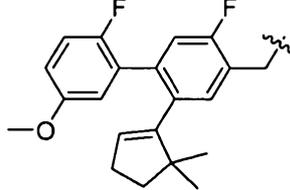
halomethyl or hydroxymethyl compound according to the methods described herein.
 Each of the compounds in the following table were prepared using the same enantiomer of the phenol.

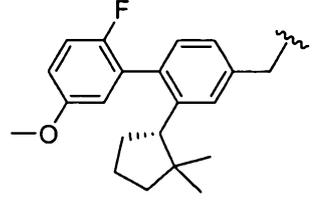
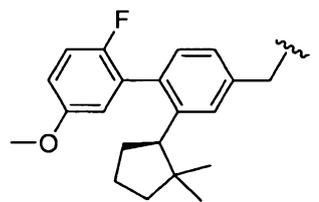
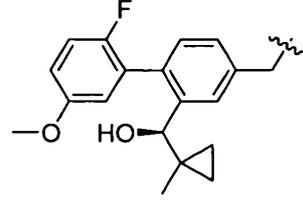
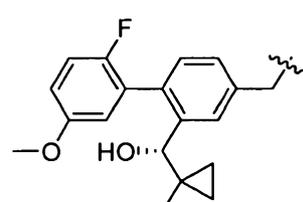
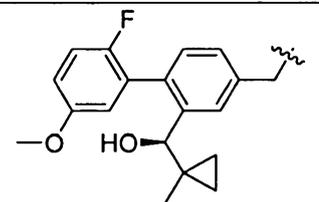
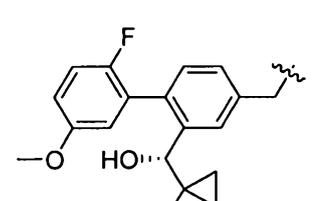
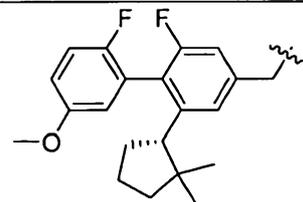
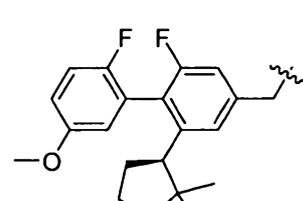
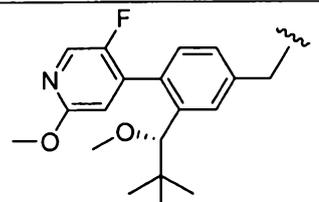
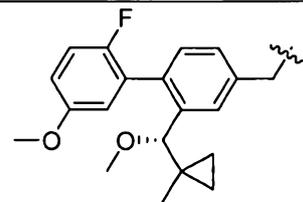
Table 17

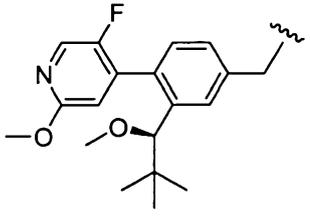
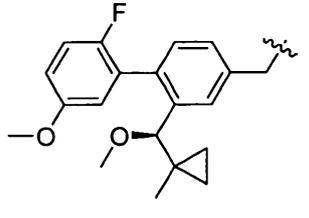
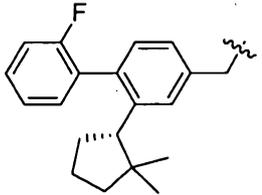
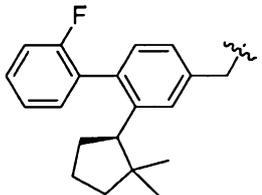
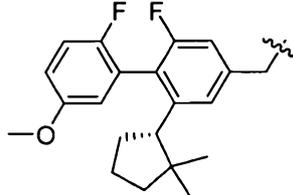
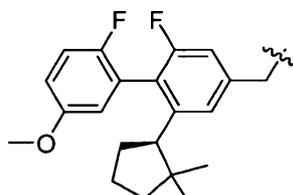
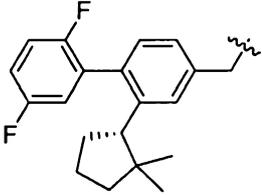
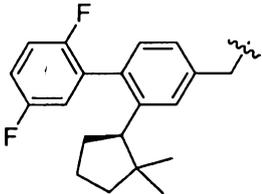
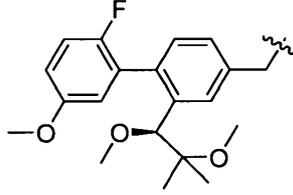
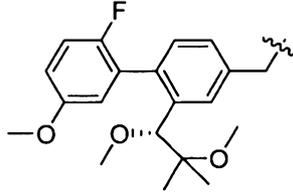
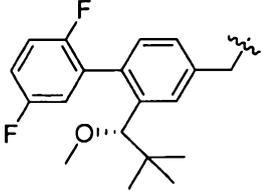
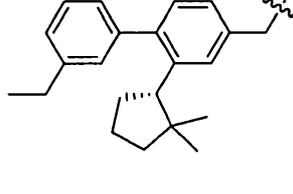


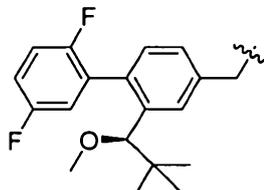
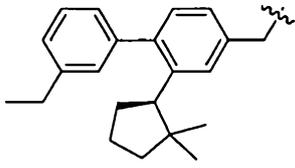
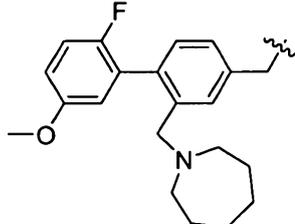
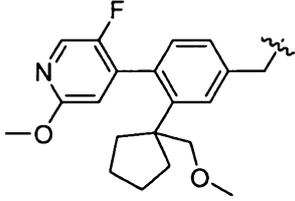
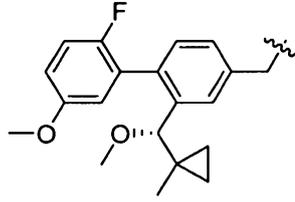
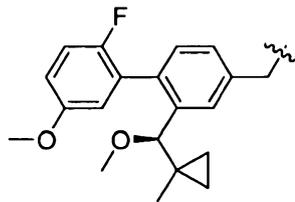
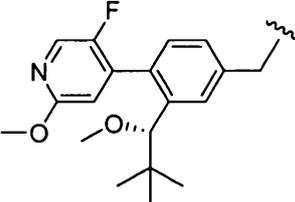
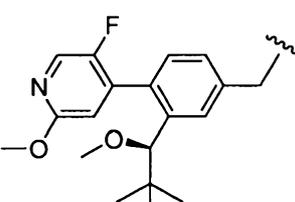
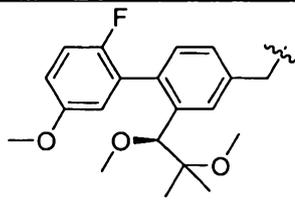
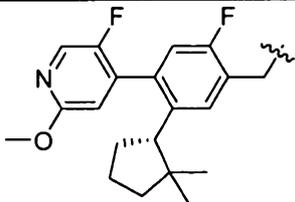
Compound	TG	Compound	TG
83.1	<p style="text-align: center;">or</p>	83.2	<p style="text-align: center;">or</p>
83.3	<p style="text-align: center;">or</p>	83.4	<p style="text-align: center;">or</p>

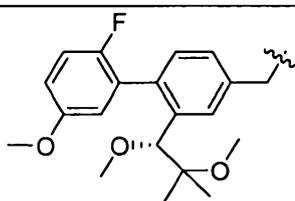
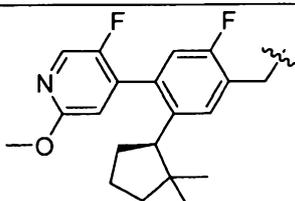
Compound	TG	Compound	TG
83.5	 <p style="text-align: center;">or</p>  <p>but not the same one as 83.4</p>	83.6	 <p style="text-align: center;">or</p> 
83.7	 <p style="text-align: center;">or</p> 	83.8	 <p style="text-align: center;">or</p> 
83.9	 <p style="text-align: center;">or</p> 	83.10	 <p style="text-align: center;">or</p> 

Compound	TG	Compound	TG
83.11	 <p style="text-align: center;">or</p> 	83.12	
83.13	 <p style="text-align: center;">or</p>  <p>but not the same one as 83.3</p>	83.14	
83.15		83.16	

Compound	TG	Compound	TG
83.17	 <p>or</p>  <p>but not the same one as 83.1</p>	83.18	 <p>or</p> 
83.19	 <p>or</p>  <p>but not the same one as 83.18</p>	83.20	 <p>or</p> 
83.21	 <p>or</p>	83.22	 <p>or</p>

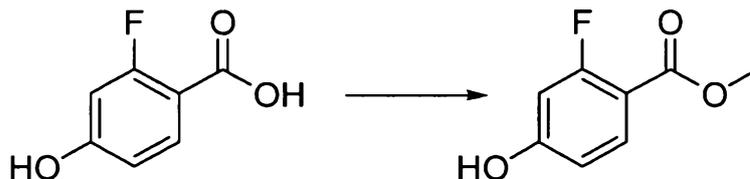
Compound	TG	Compound	TG
			
83.23	 <p style="text-align: center;">or</p> 	83.24	 <p style="text-align: center;">or</p>  <p>but not the same as 83.20</p>
83.25	 <p style="text-align: center;">or</p> 	83.26	 <p style="text-align: center;">or</p> 
83.27		83.28	

Compound	TG	Compound	TG
	<p>or</p> 		<p>or</p> 
83.29		83.30	
83.31	 <p>or</p>  <p>but not the same as 83.22</p>	83.32	 <p>or</p>  <p>but not the same as 83.21</p>
83.33	 <p>or</p>	83.34	 <p>or</p>

Compound	TG	Compound	TG
	 <p>but not the same as 83.26</p>		

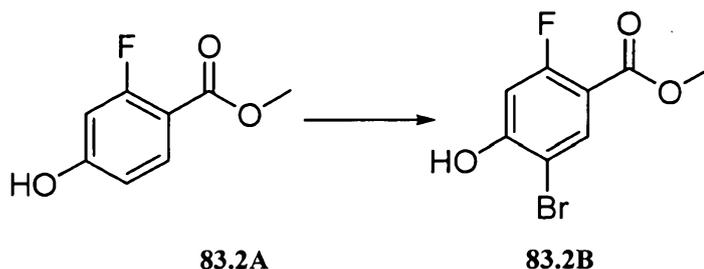
[01235] (S)-3-Cyclopropyl-3-{3-[2-((S)-2,2-dimethyl-cyclopentyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-2-fluoro-phenyl}-propionic acid or (S)-3-cyclopropyl-3-{3-[2-((R)-2,2-dimethyl-cyclopentyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-2-fluoro-phenyl}-propionic acid or (R)-3-cyclopropyl-3-{3-[2-((S)-2,2-dimethyl-cyclopentyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-2-fluoro-phenyl}-propionic acid or (R)-3-cyclopropyl-3-{3-[2-((R)-2,2-dimethyl-cyclopentyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-2-fluoro-phenyl}-propionic acid (83.1). MS ESI (neg.) m/e: 533.2 (M-H)⁺.

[01236] **Example 83.2**

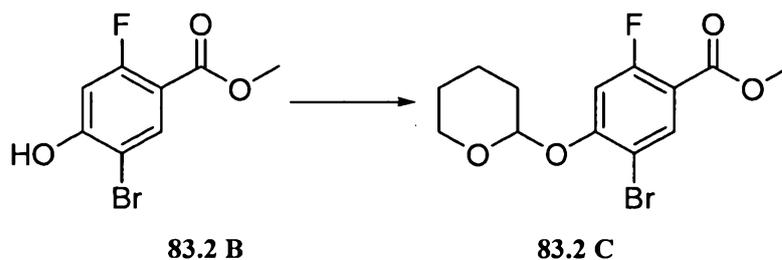


83.2A

[01237] **Methyl 2-fluoro-4-hydroxybenzoate (83.2A).** To a round bottom flask containing 2-fluoro-4-hydroxybenzoic acid (5.34 g, 34.19 mmol)(commercially available from Matrix Scientific and TCI America) was added a cold solution of MeOH (50 mL) and sulfuric acid (2.0 mL). The mixture was heated to 80°C and monitored with TLC. After 20.5 hours, the solvent was removed and diluted with diethyl ether. The organic phase was washed carefully two times with saturated aqueous NaHCO₃ and once with brine, then dried over anhydrous sodium sulfate. After filtration, the organic solvent was removed in vacuo to yield **83.2 A** as a white solid (5.82, 85%). ¹H NMR (400 MHz, DMSO-d₆) δ ppm 10.79 (1 H, s), 7.75 (1 H, t, J=8.8 Hz), 6.69 (1 H, dd, J=8.6, 2.3 Hz), 6.62 (1 H, dd, J=13.1, 2.2 Hz), 3.78 (3 H, s).

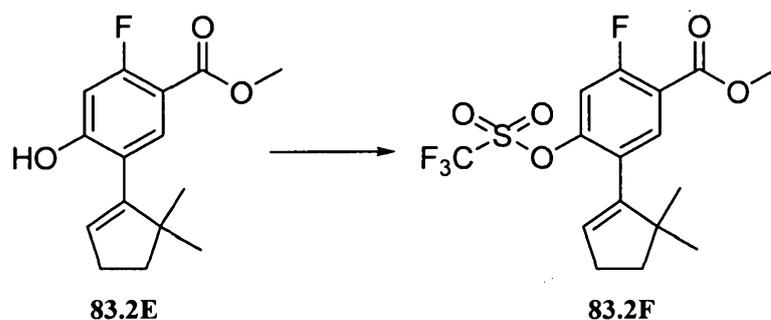


[01238] Methyl 5-bromo-2-fluoro-4-hydroxybenzoate (83.2B). To a solution of **83.2 A** (2.03 g, 11.9 mmol) in acetic acid (65 mL) was added a pre-mixed solution of bromine (0.67 mL, 13.1 mmol) in acetic acid (10 mL). The mixture was stirred at 45°C and monitored with TLC and LC-MS. After 18 hours, the reaction mixture was concentrated under reduced pressure. Brine was added to the residue, and the mixture was extracted three times with EtOAc. The combined organic layers were dried over anhydrous magnesium sulfate and then filtered and concentrated to provide **83.2B** as a white solid (2.12 g, 71 %). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.13 (1 H, d, J=7.4 Hz), 6.82 (1 H, d, J=11.3 Hz), 6.04 (1 H, s), 3.92 (3 H, s).

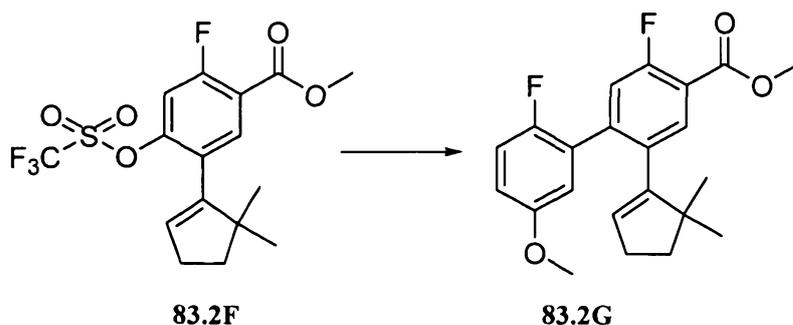


[01239] Methyl 5-bromo-2-fluoro-4-(tetrahydro-2H-pyran-2-yloxy)benzoate (83.2C). To a round bottom flask containing **83.2B** (13.15 g, 52.8 mmol) in dry DCM (90 mL) was added 3,4-dihydro-2H-pyran (10 mL, 110 mmol) followed by PPTS (0.13 g, 0.53 mmol). The reaction mixture was heated to a gentle reflux (50°C) and monitored with TLC and LC-MS. After 24 hours, the reaction was concentrated under reduced pressure and then diluted with MeOH. After concentration, the residue was heated in a round bottom flask containing MeOH on the rotary evaporator (without vacuum.) to 40°C. After about 30 minutes., the solution was concentrated to a volume of about 5 mL. After cooling to room temperature, the white solid was filtered and rinsed once with MeOH to yield **83.2C** (13.35 g, 76 %). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.25 (1 H, m), 6.96 (1 H, d, J=12.5 Hz), 5.56 (1 H, m), 3.91 (3 H, s), 3.79 (1 H, td, J=11.1, 2.5 Hz), 3.65 (1 H, d, J=10.6 Hz), 2.23 (2 H, m), 1.96 (3 H, m), 1.68 (1 H, m).

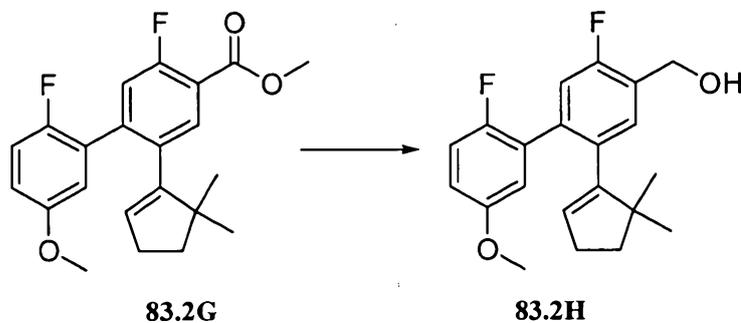
added PPTS (0.42 g, 1.69 mmol). The mixture was heated to 50°C and monitored with TLC and LCMS. After 19 hours, the organic solvent was removed under reduced pressure, then the residue was purified on silica gel (0-15% EtOAc in hexanes) to yield **83.2E** as a white solid (3.47g, 81%). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.69 (1 H, d, J=8.3 Hz), 6.71 (1 H, d, J=12.0 Hz), 5.93 (1 H, d, J=1.7 Hz), 5.80 (1 H, t, J=2.4 Hz), 3.90 (3 H, s), 2.54 (2 H, m), 1.93 (2 H, t, J=7.1 Hz), 1.11 (6 H, s).



[01242] Methyl 5-(5,5-dimethylcyclopent-1-enyl)-2-fluoro-4-(trifluoromethylsulfonyloxy)benzoate (83.2F). To a stirred solution of **83.2E** (0.80 g, 3.02 mmol) in dry DCM (15 mL) was added TEA (1.0 mL, 7.19 mmol) and 4-dimethylaminopyridine (38.1 mg, 0.312 mmol). After about 20 minutes, N-phenyl-bis(trifluoromethanesulfonimide) (1.30 g, 3.64 mmol) was added in portions. Upon complete addition, the solution was stirred at room temperature and monitored with TLC and LC-MS. After 19 hours, the organic solvent was removed under reduced pressure, and the residue was purified with silica gel chromatography using 0-10% EtOAc in hexanes to yield **83.2F** as a colorless oil (1.05 g, 88%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.84 (1 H, d, J=7.8 Hz), 7.13 (1 H, d, J=10.2 Hz), 5.79 (1 H, t, J=2.3 Hz), 3.96 (3 H, s), 2.47 (2 H, td, J=7.0, 2.3 Hz), 1.91 (2 H, t, J=7.0 Hz), 1.08 (6 H, s).

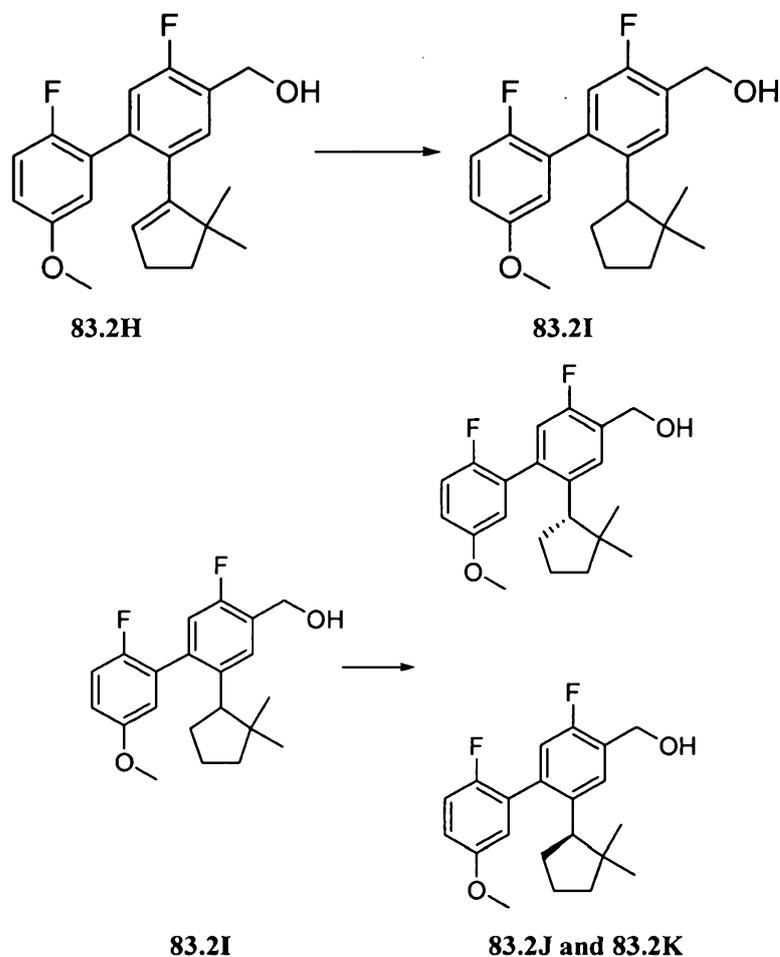


[01243] **Methyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (83.2G)**. To a stirred solution of **83.2F** (1.05 g, 2.65 mmol) in DMF (5 mL) at 23°C was added 2-fluoro-5-methoxyphenylboronic acid (0.90 g, 5.32 mmol) (commercially available from Aldrich) and potassium carbonate (1.10 g, 7.96 mmol) followed by tetrakis(triphenylphosphine)palladium (0.31 g, 0.27 mmol). The mixture was heated to 90°C. After 17 hours, the mixture was cooled to room temperature and then diluted with water. After extracting three times with EtOAc, the mixture was concentrated in vacuo and the residue was then purified on silica gel (0%-10% EtOAc/hexane) to give **83.2G** as a clear oil that was used without further purification (0.92 g, 93 %). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.79 (1 H, d, J=7.4 Hz), 7.13 (1 H, d, J=11.3 Hz), 6.99 (1 H, t, J=9.0 Hz), 6.84 (1 H, dt, J=8.7, 3.7 Hz), 6.78 (1 H, dd, J=5.9, 3.1 Hz), 5.55 (1 H, s), 3.96 (3 H, s), 3.79 (3 H, s), 2.27 (2 H, td, J=7.1, 2.5 Hz), 1.67 (2 H, t, J=7.0 Hz), 0.84 (6 H, s).



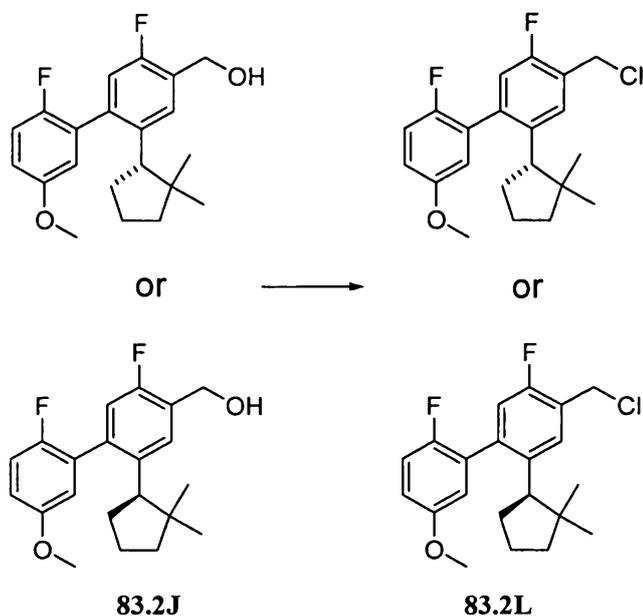
[01244] **(2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (83.2H)**. To a cooled solution of **83.2G** (0.92 g, 2.47 mmol) in dry THF (15 mL) at 0°C was added LAH, 1.0 M in THF (5.0 mL, 5.0 mmol) dropwise. Upon complete addition, the reaction was maintained at 0°C and was monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction (gas evolution occurred). The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was then purified by flash chromatography (SiO₂ gel 60, eluted with 0%-50% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **83.2H** as a colorless oil (0.70 g, 82 %). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.30 (1 H, m), 7.05 (1 H, dd, J=10.6, 1.1 Hz), 6.97 (1 H, t, J=8.9 Hz), 6.83

(2 H, m), 5.52 (1 H, td, J=2.4, 0.9 Hz), 4.81 (2 H, s), 3.76 (3 H, s), 2.25 (2 H, td, J=7.1, 2.4 Hz), 1.76 (1 H, br. s.), 1.69(2 H, m), 0.85 (6 H, s).

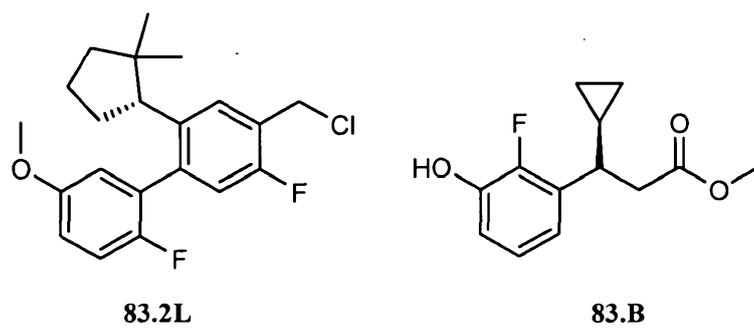
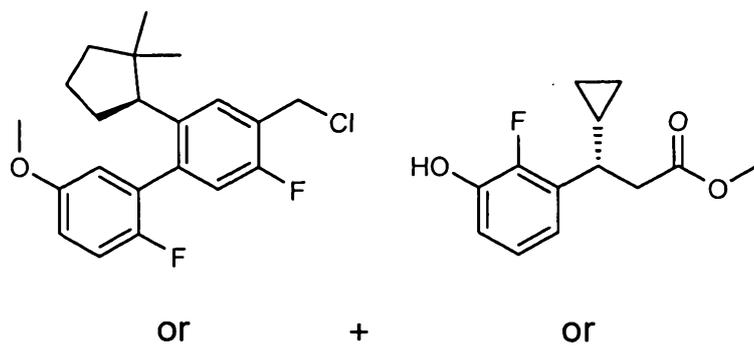


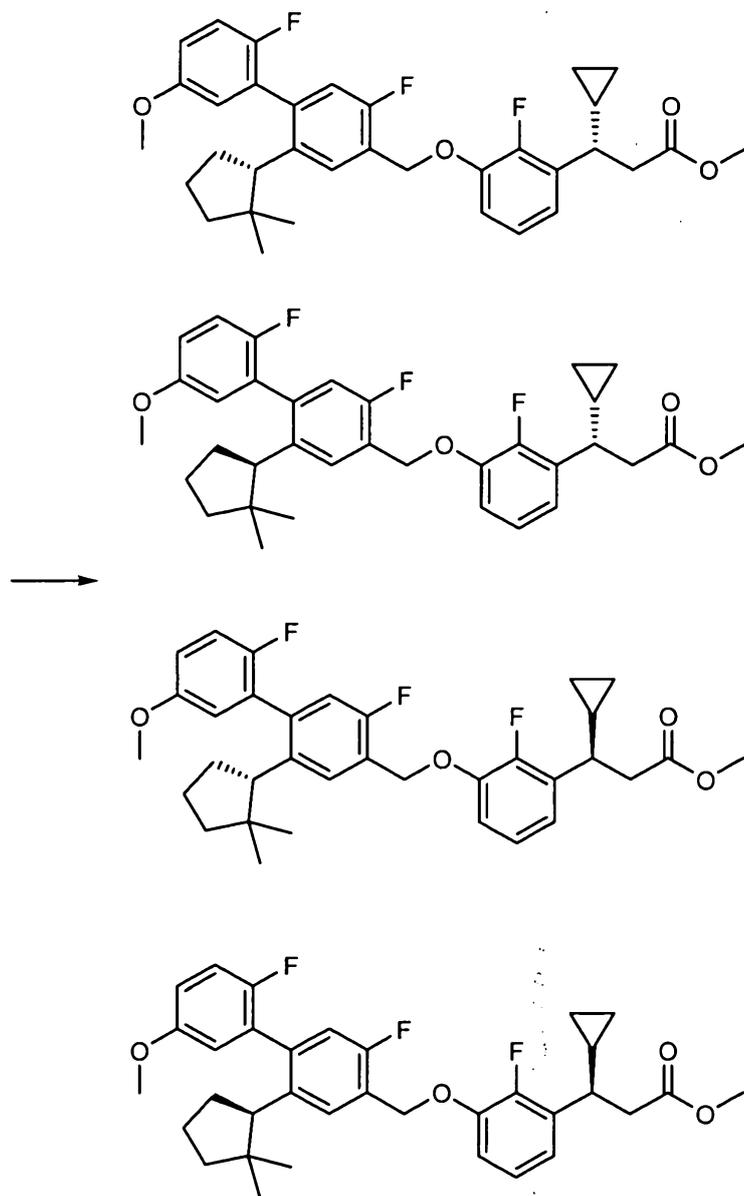
[01245] (2-(2,2-Dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (**83.2I**). To a dry flask containing **83.2H** (0.70 g, 2.03 mmol) in dry MeOH (5 mL) and EtOAc (3 mL) was added palladium, 10wt. % on activated carbon (77.2 mg). After purging, the mixture was stirred under an atmosphere of hydrogen at room temperature. After 4.5 hours, the mixture was filtered through Celite. After concentration, the residue was identified as **83.2I** as a mixture of enantiomers and rotamers (0.31 g, 45 %). Chiral separation of **83.2 I** was accomplished on Chiracel-OJ (2% IPA in hexane) to provide **83.2J** (peak 1) and **83.2K** (peak 2). Both enantiomers were used to synthesize example compounds, and both enantiomers gave active

compounds. The enantiomer corresponding to peak 1 provided the more active example compound.



[01246] **4-(Chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl (83.2L).** To a solution of **83.2J** (0.71 g, 2.05 mmol) in dry DCM (23 mL) and dry DMF (0.18 mL) was added thionyl chloride (0.3 mL, 4.1 mmol) dropwise at 0°C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to yield **83.2L** as a colorless oil (0.73 g, 97%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.46 (1 H, m), 7.11 (3 H, m), 6.75 (1H, m), 4.78 (2 H, m), 3.80 (3 H, s), 2.91 (1 H, m), 2.20 (2 H, m), 1.87 (2 H, m), 1.59 (1 H, m), 1.43 (1 H, m), 0.77 (3 H, m), 0.64 (3 H, m).

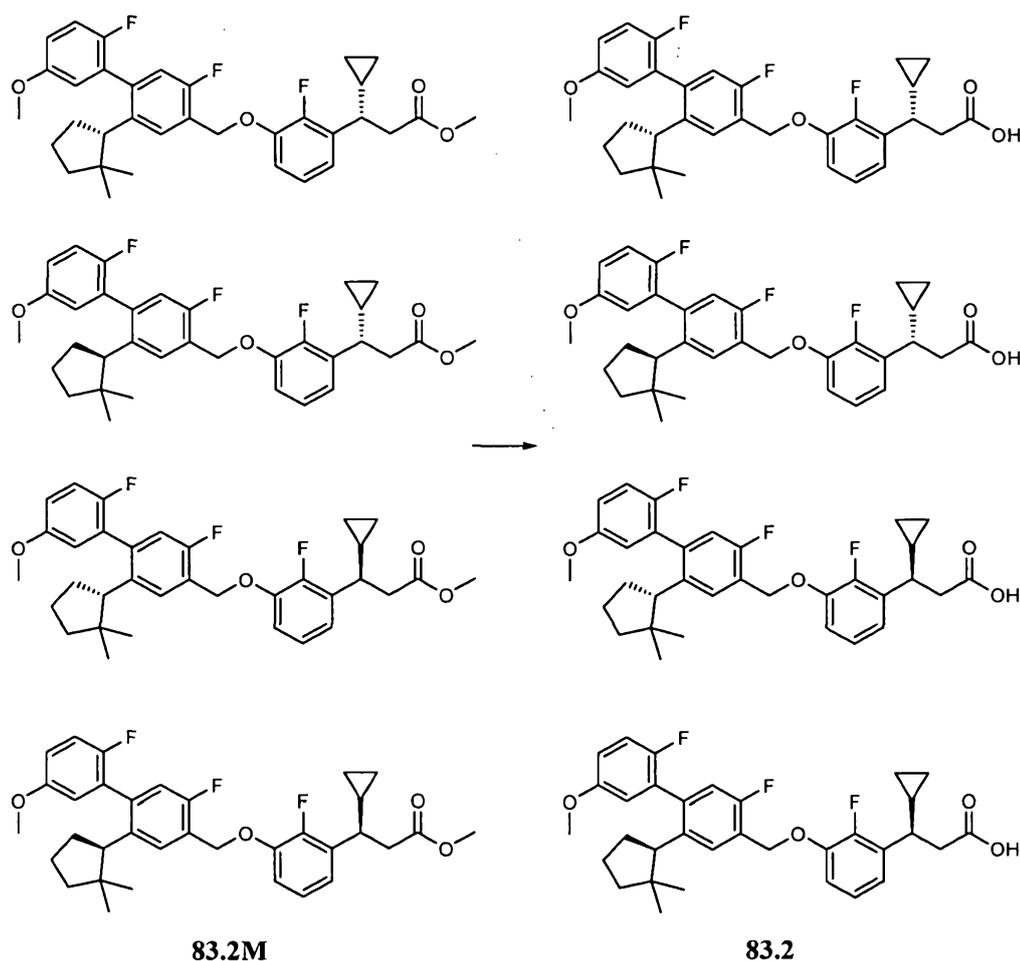




83.2M

[01247] Methyl (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoate or methyl (3S)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-

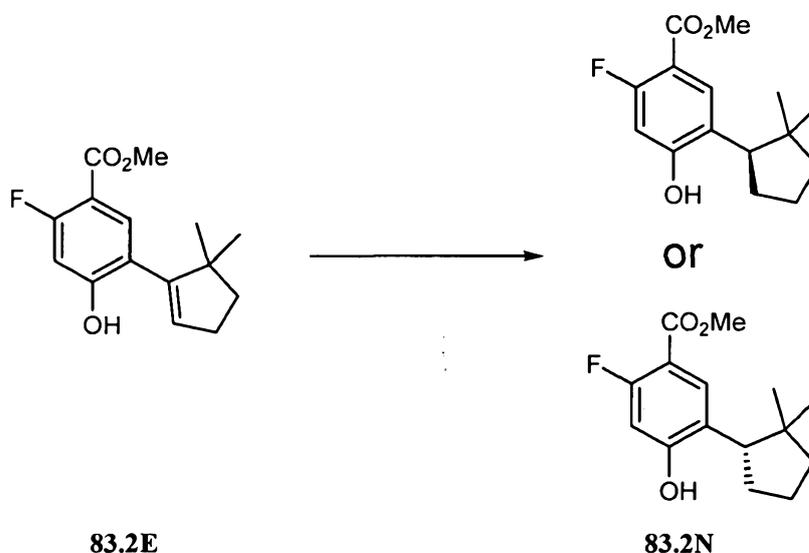
dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoate (83.2 M). To a flask containing **83.B** (445.9 mg, 1872 μ mol) and cesium carbonate (792.7 mg, 2433 μ mol) in DMF (10 mL) was added **83.2 L** (717.0 mg, 1965 μ mol), and the mixture was stirred overnight. The reaction was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, concentrated, and then purified by silica gel chromatography (0 to 20% EtOAc/ Hexanes) to provide **83.2M** (992.3 mg, 93.57% yield).



[01248] (S)-3-Cyclopropyl-3-{3-[2-((S)-2,2-dimethyl-cyclopentyl)-5,2'-difluoro-5'-methoxy-biphenyl-4-ylmethoxy]-2-fluoro-phenyl}-propionic acid or (S)-3-cyclopropyl-3-{3-[2-((R)-2,2-dimethyl-cyclopentyl)-5,2'-difluoro-5'-methoxy-biphenyl-4-ylmethoxy]-2-fluoro-phenyl}-propionic acid or (R)-3-cyclopropyl-3-{3-[2-((S)-2,2-dimethyl-cyclopentyl)-5,2'-difluoro-5'-methoxy-biphenyl-4-ylmethoxy]-2-fluoro-phenyl}-propionic acid or (R)-3-cyclopropyl-3-{3-[2-((R)-2,2-dimethyl-

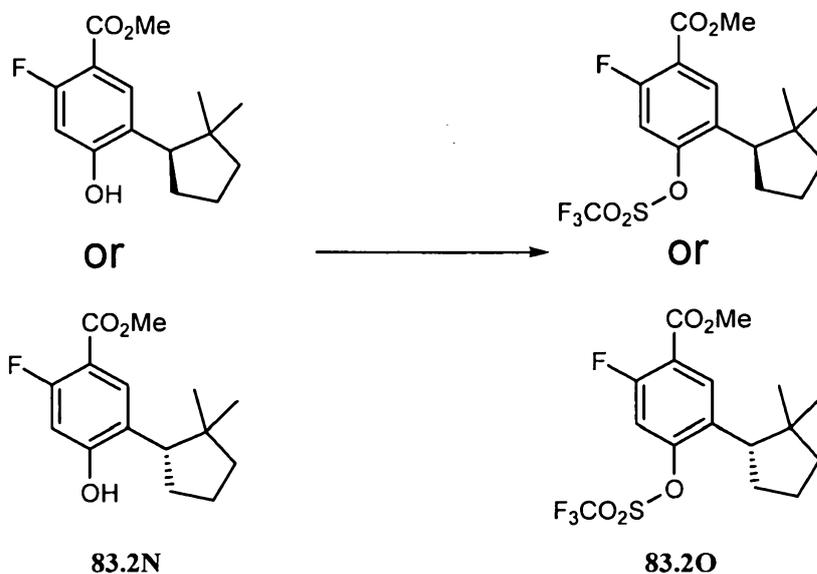
cyclopentyl)-5,2'-difluoro-5'-methoxy-biphenyl-4-ylmethoxy]-2-fluoro-phenyl}-propionic acid (83.2). To a solution of **83.2M** (992.3 mg, 1.8 mmol) in THF/MeOH (2/1) (15 mL) was added LiOH (5.000 mL, 5.0 mmol). The resulting mixture was stirred overnight at 23°C, quenched with excess 1N HCl, and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated. The crude residue was purified by silica gel chromatography (5 to 25% EtOAc/hexanes) to afford **83.2** (0.93 g, 96% yield). MS ESI (neg.) m/e: 551.2 (M-H).

[01249] **Asymmetric synthesis of 83.2J.** The following procedures were used to synthesize **83.2J** using a highly enantioselective procedure to hydrogenate **83.2E** to form **83.2N**.

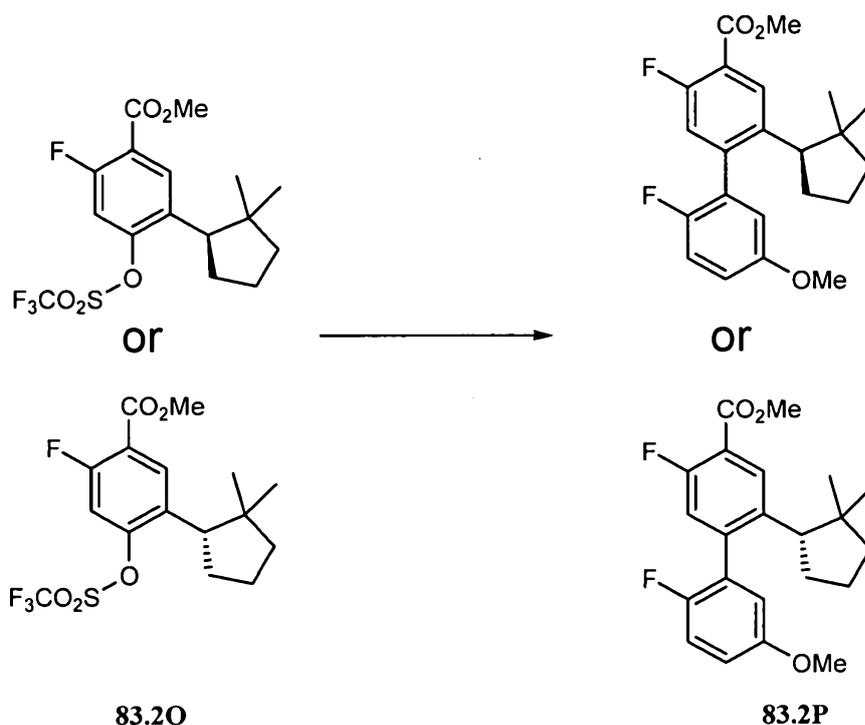


[01250] **(R)-Methyl 5-(2,2-dimethylcyclopentyl)-2-fluoro-4-hydroxybenzoate or (S)-methyl 5-(2,2-dimethylcyclopentyl)-2-fluoro-4-hydroxybenzoate (83.2N).** A mixture of Rh(COD)₂BF₄ (Stern Chemical, 35138-22-8, 36.95 mg, 0.091 mmol) and (R)-1-[(S)-2-(R)-(Ditertbutylphosphino)ferrocenyl]ethyl-bis-(3,5-bistrifluoromethylphenyl)phosphine (Solvias, SL-J210-1, 81.5 mg, 0.100 mmol) in THF (75 mL) was stirred under N₂ for 60 minutes and a dark red solution formed. To the resulting solution was added methyl 5-(5,5-dimethylcyclopent-1-enyl)-2-fluoro-4-hydroxybenzoate **83.2E** (8.2g, 45.4 mmol) and TEA (10mol%, 0.63 mL, 4.54 mmol). The resulting solution was filled with H₂ (200psi) three times and stirred at room temperature/200psi for 2 hours. The resulting mixture was passed through a short plug of

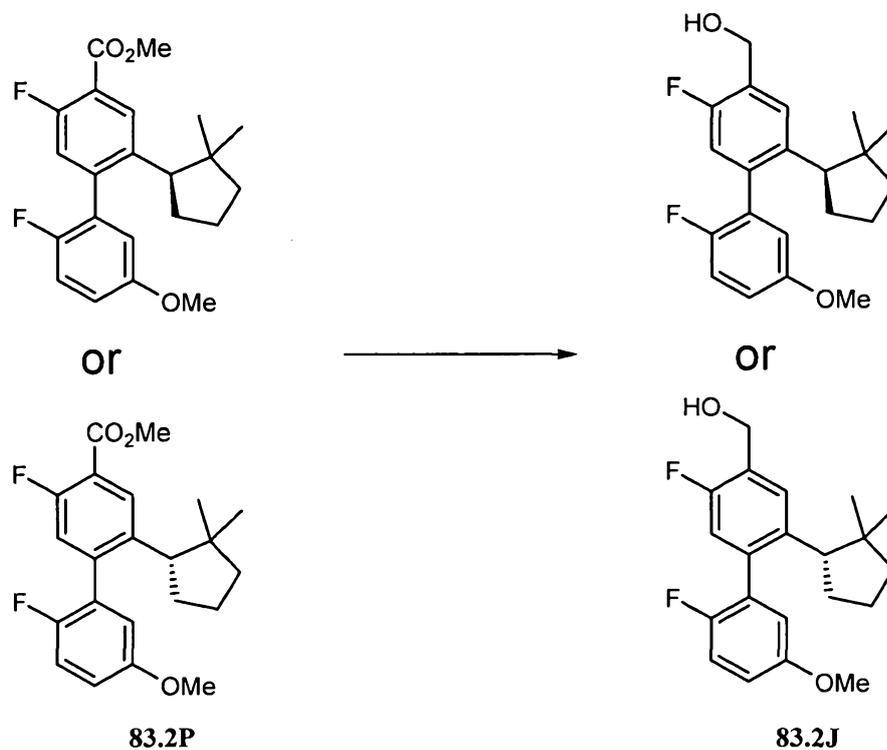
silica gel, eluting with 1:1 hexane/EtOAc. The mixture was then concentrated affording the desired product as a white solid (83% yield (6.8 g), 99.3% ee).



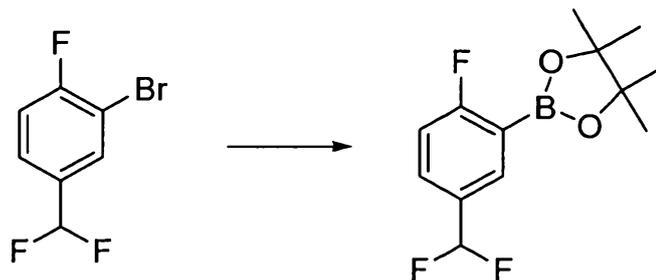
[01251] (R)-Methyl 5-(2,2-dimethylcyclopentyl)-2-fluoro-4-(trifluoromethylsulfonyloxy)benzoate or (S)-methyl 5-(2,2-dimethylcyclopentyl)-2-fluoro-4-(trifluoromethylsulfonyloxy)benzoate (83.2O). To a stirred solution of **83.2N** (4.02 g, 15.1 mmol) in dry DCM (50 mL) was added TEA (4.2 mL, 30.2 mmol) and DMAP (0.19 g, 1.52 mmol). After 20 minutes, N-phenyl-bis(trifluoromethanesulfonimide) (5.94 g, 16.6 mmol) was added in portions. Upon complete addition, the solution was stirred at room temperature and monitored with TLC and LC-MS. After 4 hours, the mixture was washed twice with brine and then dried over anhydrous magnesium sulfate. After filtration and concentration, the residue was purified with silica gel chromatography (0-10% EtOAc in hexanes) to yield **83.2O** as a colorless oil (5.51, 92%). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.97 (1 H, d, J=7.8 Hz), 7.14 (1 H, d, J=10.0 Hz), 3.96 (3 H, s), 3.13 (1 H, dd, J=10.1, 8.2 Hz), 2.14 (2 H, m), 1.96 (2 H, m), 1.70 (2 H, m), 1.00 (3 H, s), 0.69 (3 H, s).



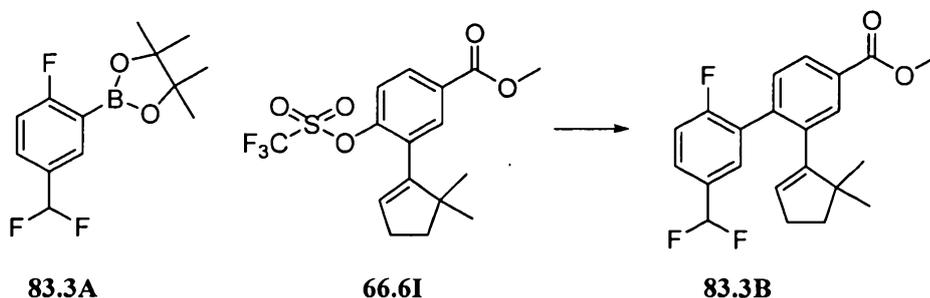
[01252] **Methyl 2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate or methyl 2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (83.2P).** To a stirred solution of **83.2O** (5.51 g, 13.8 mmol) in DMF (25 mL) at 23°C was added 2-fluoro-5-methoxyphenylboronic acid (4.71 g, 27.7 mmol) (commercially available from Aldrich) and potassium carbonate (5.74 g, 41.6 mmol) followed by tetrakis(triphenylphosphine)palladium (1.60 g, 1.39 mmol). The mixture was heated to 90°C. After 3.5 hours, the mixture was cooled to room temperature and then diluted with water. After extracting three times with EtOAc, the mixture was concentrated in vacuo and then purified on silica gel (0%-10% EtOAc/hexane) to yield **83.2P** as an oil that solidified (5.11 g, 99%).



[01253] (2-((1R)-2,2-Dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol or (2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol (**83.2J**). To a cooled solution of **83.2P** (5.11 g, 13.6 mmol) in dry THF (40 mL) at 0°C was added LAH (1.0 M in THF)(27.3 mL, 27.30 mmol) dropwise. Upon complete addition, the reaction was maintained at 0°C and was monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction (gas evolution occurred). The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified by silica gel chromatography (0-25% EtOAc in hexanes) to yield **83.2J** as a colorless oil (3.94 g, 83 %). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.50 (1 H, m), 7.11 (3 H, m), 6.85 (1H, m), 4.81 (2 H, s), 3.80 (3 H, s), 2.92 (1H, m), 2.19 (2 H, m), 1.83 (1 H, m), 1.72 (1 H, m), 1.59 (2 H, m), 1.42 (1 H, m), 0.82 (3 H, m), 0.65 (3 H, m).

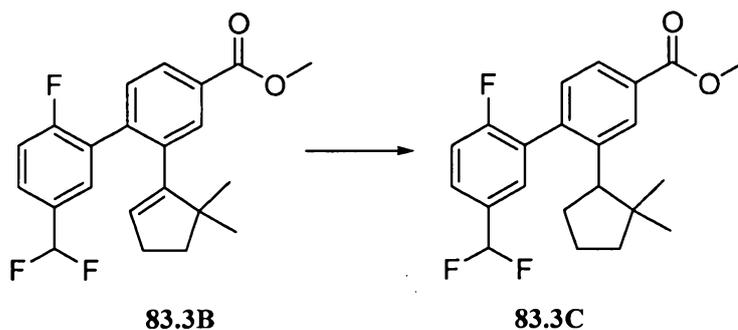
[01254] Example 83.3**83.3A**

[01255] 2-(5-(Difluoromethyl)-2-fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (83.3A). A stirred mixture of 1-bromo-5-difluoromethyl-2-fluorobenzene (available from Oakwood Products, Inc.) (2.02 g, 8.99 mmol), bis(pinacolato)diboron (2.51 g, 9.89 mmol), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) DCM adduct (368.8 mg, 0.45 mmol), and potassium acetate (2.65 g, 27.01 mmol) in dry 1,4-dioxane (35 mL) was purged three times with argon and placed under vacuum three times. The mixture was heated to 90°C and monitored with LC-MS and TLC. After 18 hours, the reaction was cooled to room temperature and then filtered through Celite. The organic solvent was removed under reduced pressure, and the residue was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to yield **83.3A** as a colorless oil (1.60 g, 65 %). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.89 (1 H, td, J=2.7, 1.2 Hz), 7.63 (1 H, m), 7.09 (1 H, t, J=8.6 Hz), 6.62 (1H, t), 1.35 (12 H, s).

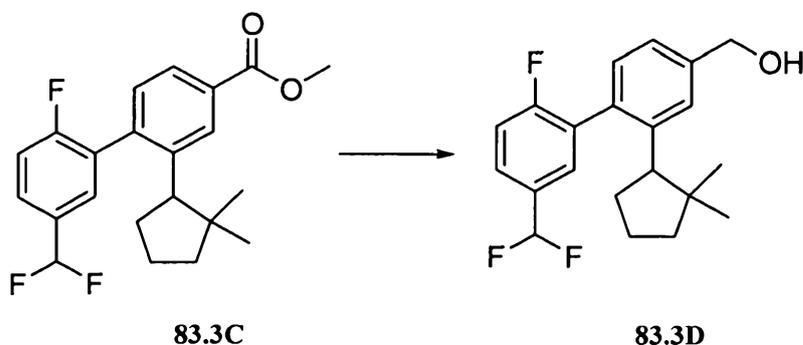
**83.3A****66.6I****83.3B**

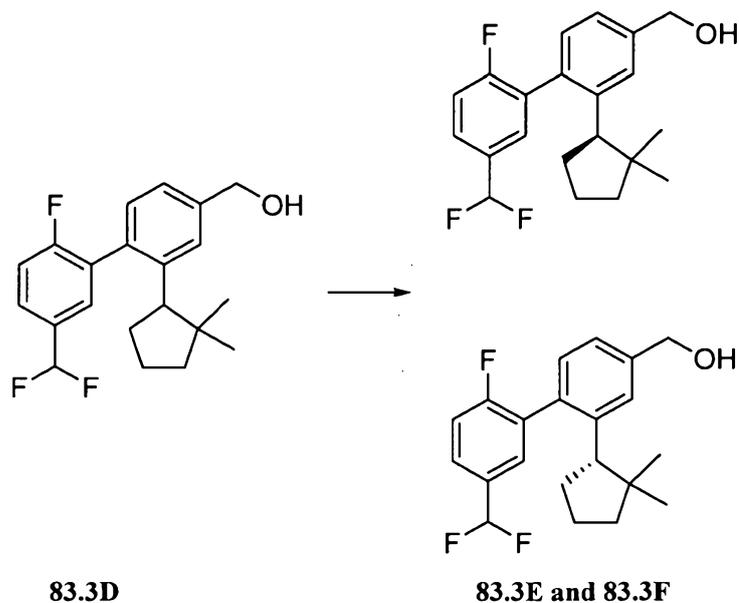
[01256] Methyl 5'-(difluoromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-carboxylate (83.3B). To a stirred solution of **66.6 I** (1.12 g, 2.96 mmol) in DMF (10 mL) at 23°C was added potassium carbonate (1.23 g, 8.87 mmol) followed by tetrakis(triphenylphosphine)palladium (0.34 g, 0.29 mmol). The mixture was purged three times with argon and placed under vacuum three times. Before heating, **83.3A** (1.60 g, 5.89 mmol) was added via syringe, and then the mixture was heated to

90°C. After 19 hours, the mixture was cooled to room temperature and then diluted with water. After extracting three times with EtOAc, the mixture was concentrated in vacuo and then purified on silica gel (0%-10% EtOAc/hexane) to give **83.3B** as a clear oil (0.99, 90 %). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.00 (1 H, dd, J=8.0, 1.8 Hz), 7.94 (1 H, d, J=1.6 Hz), 7.50 (3 H, m), 7.16 (1 H, t, J=9.0 Hz), 6.63 (1H, t), 5.53 (1 H, s), 3.96 (3 H, s), 2.25 (2 H, td, J=7.0, 2.3 Hz), 1.65 (2 H, t, J=7.0 Hz), 0.85 (6 H, s).

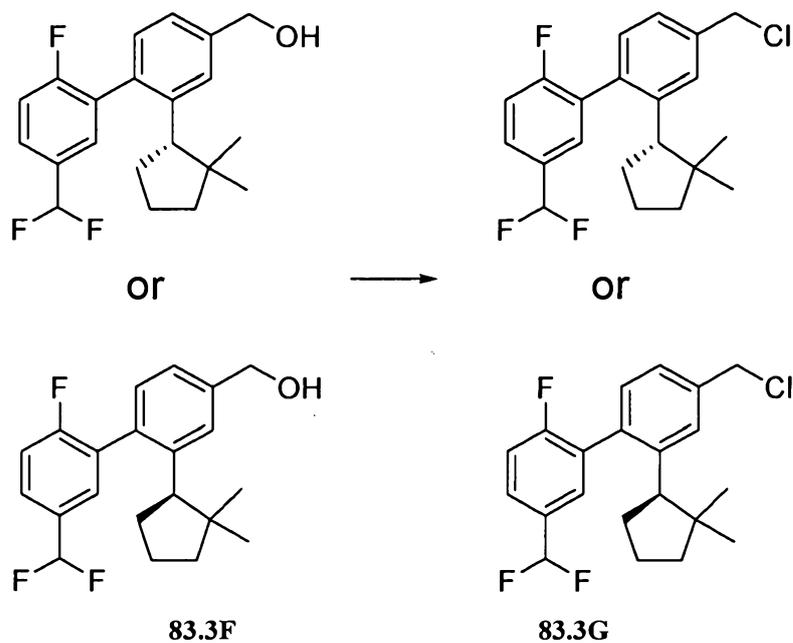


[01257] **Methyl 5'-(difluoromethyl)-2-(2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-carboxylate (83.3C)**. To a dry flask containing **83.3B** (0.86 g, 2.30 mmol) in MeOH (10 mL) and EtOAc (2 mL) was added palladium, 10% wt on activated carbon (0.25 g, 0.23 mmol). After purging, the mixture was stirred under an atmosphere of hydrogen at room temperature. The reaction was monitored with TLC and LC-MS. After 22.5 hours, the reaction was filtered through Celite. After concentration, the residue was identified **83.3C** and used without purification (0.86 g, 99%). MS ESI (pos.) m/e: 376.9 (M+H)⁺.



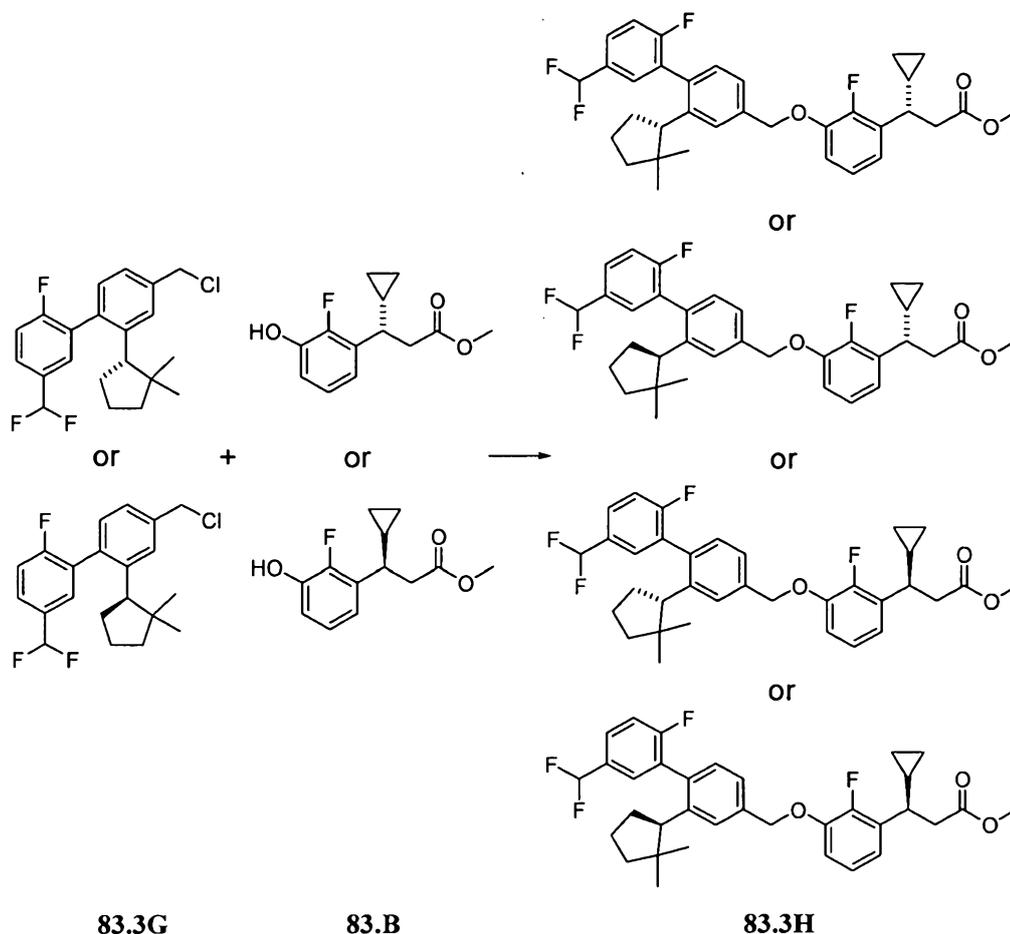


[01258] **(S')-(Difluoromethyl)-2-(2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methanol (83.3D)**. To a cooled solution of **83.3C** (0.86 g, 2.29 mmol) in dry THF (15 mL) at 0 °C was added LAH, 1.0M in THF (4.6 mL, 4.6 mmol) dropwise. Upon complete addition, the reaction was maintained at 0 °C and monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction (gas evolution occurred). The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified by flash chromatography (SiO₂ gel 60, eluted with 0%-100% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide **83.3D** as a colorless oil (0.62 g, 77 %). MS ESI (pos.) m/e: 331.0 (M-H₂O)⁺. Chiral separation of **83.3D** was accomplished on Chiracel-OD (4% IPA in hexane) to provide **83.3E** (peak 1) and **83.3F** (peak 2). Both enantiomers were used to synthesize example compounds, and both enantiomers gave active compounds. The enantiomer corresponding to peak 2 provided the more active example compound.



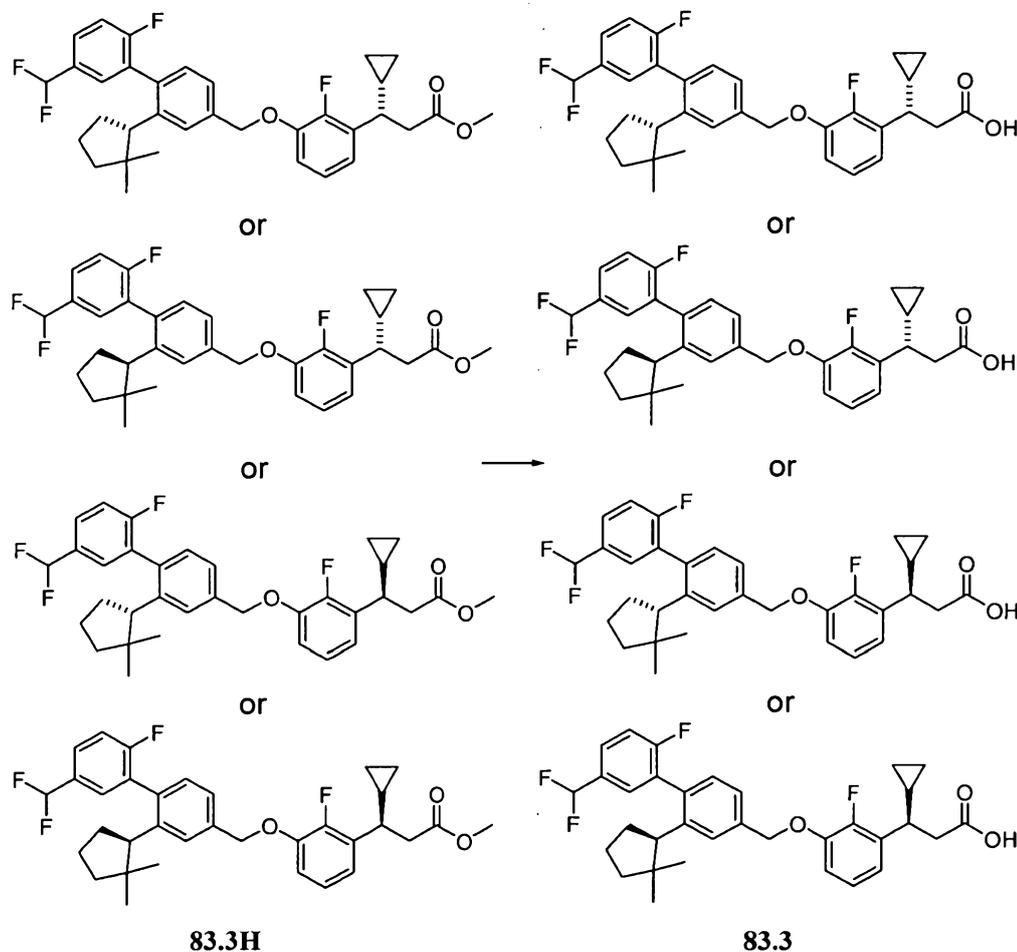
[01259] 4-(Chloromethyl)-5'-(difluoromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl or 4-(chloromethyl)-5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl (**83.3G**).

To a solution of **83.3F** (0.29 g, 0.83 mmol) in dry DCM (10.5 mL) and dry DMF (0.08 mL) was added thionyl chloride (0.12 mL, 1.65 mmol) at 0°C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 45 minutes, the reaction was concentrated then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to yield **83.3G** (0.27 g, 90 %).



[01260] **Methyl (3S)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoate or methyl (3S)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoate (83.3H).** To a vial containing **83.B** (34.9 mg, 0.146 mmol) in 1.0 mL dry DMF was added cesium carbonate (58.6 mg, 0.180 mmol). The mixture was stirred at room temperature for 10 minutes, and then **83.3G** (60.7 mg, 0.165 mmol) was added. After 22 hours, the reaction was diluted with water and then extracted five times with EtOAc. The combined organic layers were then washed with brine and dried over anhydrous magnesium sulfate. The solid was filtered off, and the solvent was

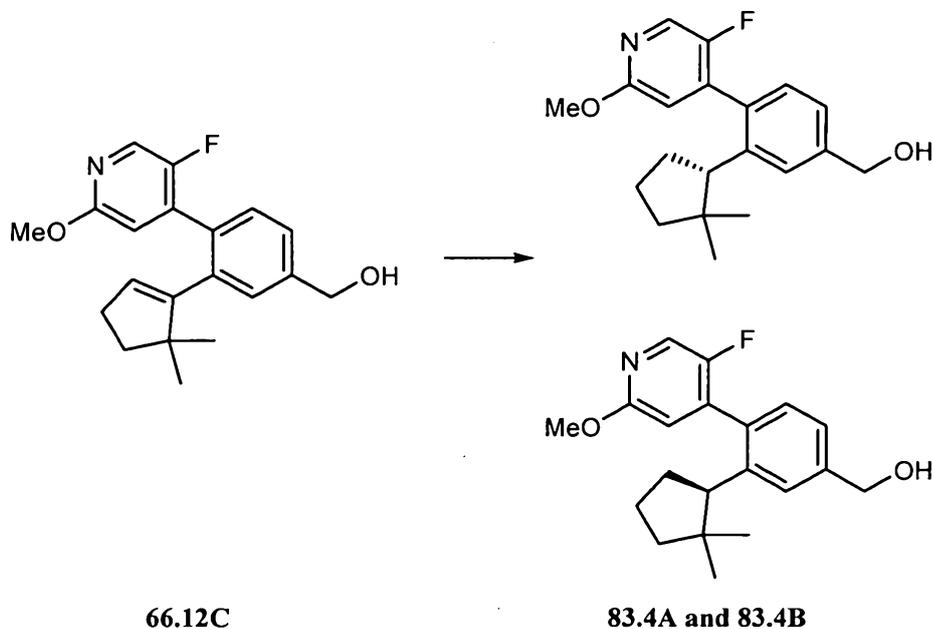
concentrated. The residue was purified by silica gel flash chromatography (0-5% EtOAc/hexane) to yield **83.3H** (77.7 mg, 93.3 %). MS ESI (pos.) m/e: 568.9 (M+H)⁺.



[01261] (3S)-3-Cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid (**83.3**). A pre-mixed solution of 2 M NaOH (0.5 mL, 1.00 mmol), THF (1 mL), and MeOH (1 mL) was added to a vial containing **83.3H** (77.7 mg, 0.137 mmol). This solution was stirred at room temperature and monitored with TLC and

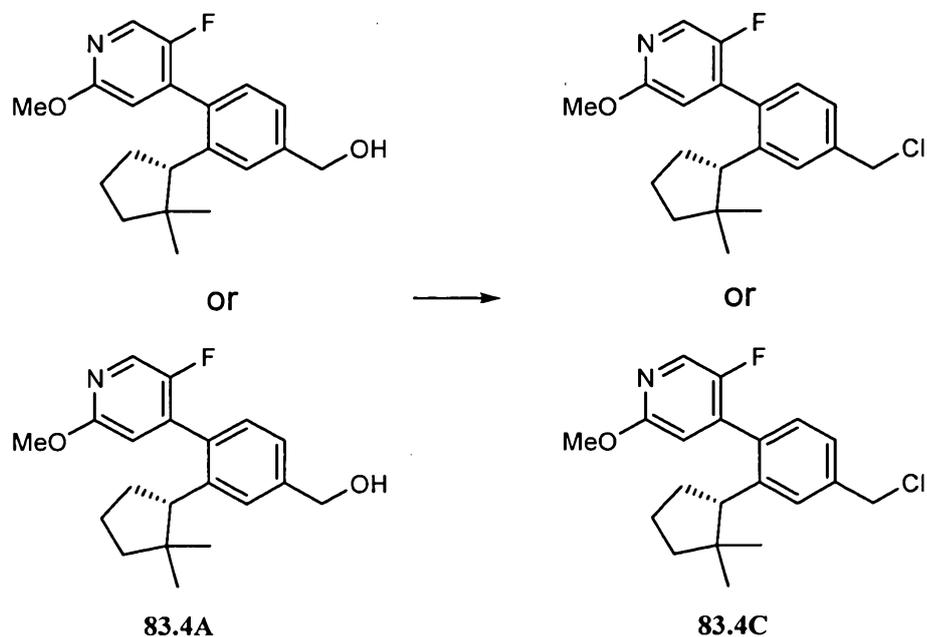
LC-MS. After 24 hours, the mixture was diluted with water and acidified with 1 M aqueous HCl solution, then extracted five times with EtOAc. The organic phase was dried over anhydrous magnesium sulfate and then filtered and concentrated. The residue was purified with reverse phase HPLC using 30-90% Solvent B to yield **83.3** which was lyophilized (38.2 mg, 50%). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.55 (4 H, m), 7.30 (2 H, m), 7.04 (1 H, m), 6.96 (2 H, m), 6.81 (1H, t), 5.18 (2 H, m), 2.92 (2 H, m), 2.77 (1 H, m), 2.24 (2 H, m), 1.89 (1 H, m), 1.74 (1 H, m), 1.56 (1 H, m), 1.40 (1 H, m), 1.20 (1 H, m), 0.72 (4 H, m), 0.50 (2 H, m), 0.47 (1 H, m), 0.34 (1 H, dq, J=9.6, 4.8 Hz), 0.25 (1 H, m). MS ESI (neg.) m/e: 552.8 (M-H)⁺.

[01262] **Example 83.4**

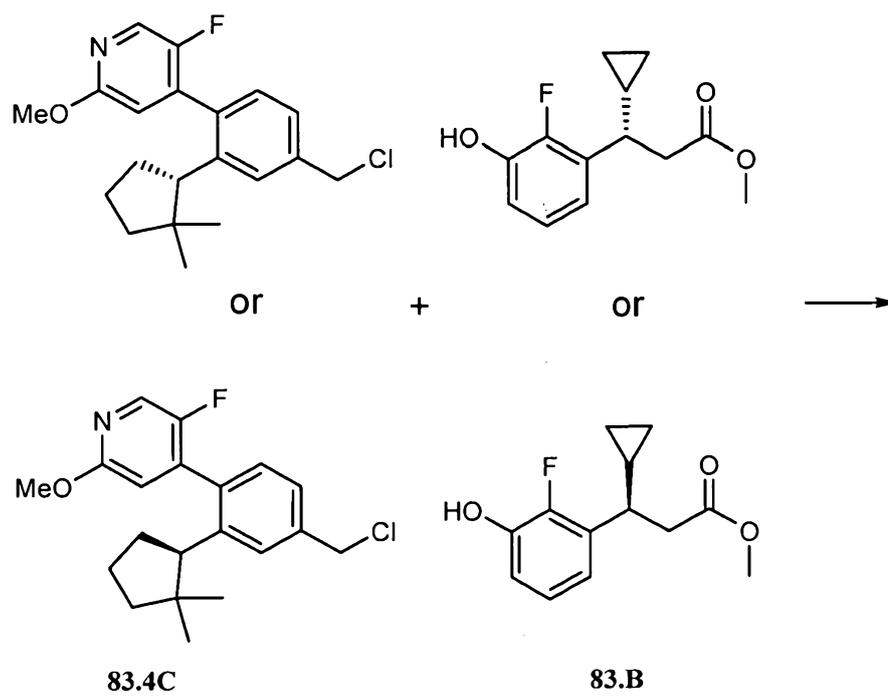


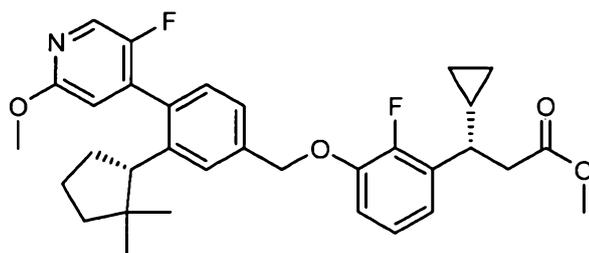
[01263] **(3-((S)-2,2-Dimethylcyclopentyl)-4-(5-fluoro-2-methoxy-pyridin-4-yl)phenyl)methanol and (3-((R)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-methoxy-pyridin-4-yl)phenyl)methanol (83.4A and 83.4B)**. To a flask with (3-(5,5-dimethylcyclopent-1-enyl)-4-(5-fluoro-2-methoxy-pyridin-4-yl)phenyl)methanol **66.12C** (50 mg, 0.153 mmol) was added 10 mg 10% Pd on Carbon, 1.2 mL EtOAc and 1.2 mL MeOH. The flask was purged with hydrogen and then stirred under a hydrogen balloon for 2 hours. LC/MS showed the completion of the reaction. The reaction was filtered through a pad of Celite and rinsed with EtOAc. Two additional reactions were run with the same condition on 70 mg and 81 mg scale. Then the three batches of the reactions (a

total of 201 mg of **66.12C**) were combined and purified on chiral OD column in four equal portions with 3% IPA/Hexanes to afford **83.4A** (54 mg, 98% ee, the later-eluting enantiomer) and **83.4B** (78 mg, 100% ee). The mixed fraction was repurified on chiral column to afford an additional 28 mg of **83.4A** (>99% ee).

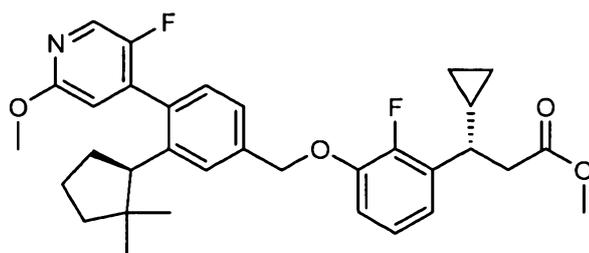


[01264] **4-(4-(Chloromethyl)-2-((S)-2,2-dimethylcyclopentyl)phenyl)-5-fluoro-2-methoxypyridine or 4-(4-(chloromethyl)-2-((R)-2,2-dimethylcyclopentyl)phenyl)-5-fluoro-2-methoxypyridine (83.4C)**. The same procedure used to prepare **66.12D** from **66.12C** was applied to make **83.4C** from **83.4A** (28 mg, >99% ee). Compound **83.4C** was obtained as an oil (27 mg, 91%).

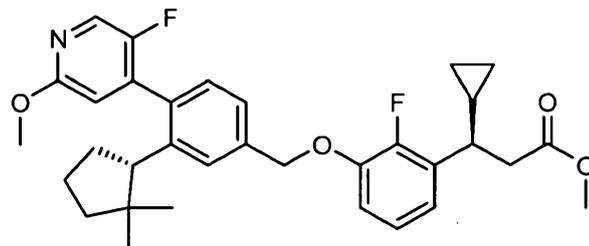




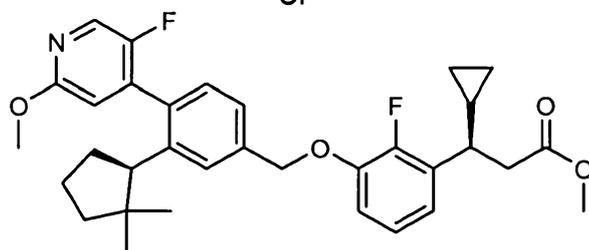
or



or

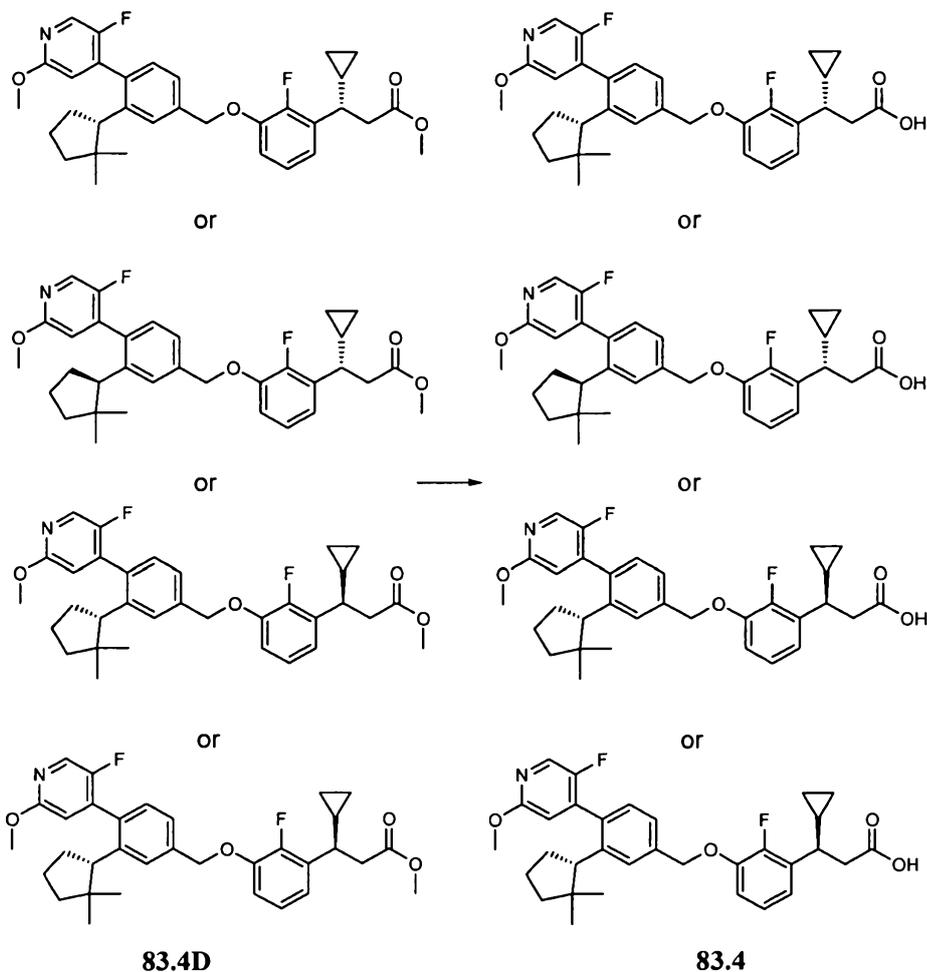


or

**83.4D**

[01265] **Compound 83.4D.**

[01266] To **83.4C** (27 mg, 78 μmol) was added **83.B** (25 mg, 105 μmol) and then cesium carbonate (51 mg, 155 μmol). DMF 1.2 mL was added and the reaction was stirred overnight. Water was added and the reaction was extracted with EtOAc. Silica gel chromatography afforded **83.4D** 42 mg (98%).



[01267] (S)-3-Cyclopropyl-3-{3-[3-((S)-2,2-dimethyl-cyclopentyl)-4-(5-fluoro-2-methoxy-pyridin-4-yl)-benzyloxy]-2-fluoro-phenyl}-propionic acid or (S)-3-cyclopropyl-3-{3-[3-((R)-2,2-dimethyl-cyclopentyl)-4-(5-fluoro-2-methoxy-pyridin-4-yl)-benzyloxy]-2-fluoro-phenyl}-propionic acid or (R)-3-cyclopropyl-3-{3-[3-((S)-2,2-dimethyl-cyclopentyl)-4-(5-fluoro-2-methoxy-pyridin-4-yl)-benzyloxy]-2-fluoro-phenyl}-propionic acid or (R)-3-cyclopropyl-3-{3-[3-((R)-2,2-dimethyl-cyclopentyl)-4-(5-fluoro-2-methoxy-pyridin-4-yl)-benzyloxy]-2-fluoro-phenyl}-propionic acid (83.4). Compound 83.4 was prepared from 42 mg of 83.4D according to the method of preparing 66.12 from 66.12E. Silica gel chromatography afforded 39 mg (95%) of 83.4. MS ESI (neg.) m/e: 534.2 (M-H)⁺.

[01268] (S)-3-Cyclopropyl-3-{3-[3-((R)-2,2-dimethyl-cyclopentyl)-4-(5-fluoro-2-methoxy-pyridin-4-yl)-benzyloxy]-2-fluoro-phenyl}-propionic acid or (S)-3-cyclopropyl-3-{3-[3-((S)-2,2-dimethyl-cyclopentyl)-4-(5-fluoro-2-methoxy-pyridin-4-yl)-benzyloxy]-2-fluoro-phenyl}-propionic acid or (R)-3-cyclopropyl-3-{3-[3-((R)-2,2-dimethyl-cyclopentyl)-4-(5-fluoro-2-methoxy-pyridin-4-yl)-benzyloxy]-2-fluoro-phenyl}-propionic acid or (R)-3-cyclopropyl-3-{3-[3-((S)-2,2-dimethyl-cyclopentyl)-4-(5-fluoro-2-methoxy-pyridin-4-yl)-benzyloxy]-2-fluoro-phenyl}-propionic acid (83.5). Compound 83.5 was prepared using the same method used to prepare compound 83.4 starting from 83.4B (peak one). MS ESI (neg.) m/e: 534.2 (M-H)⁺.

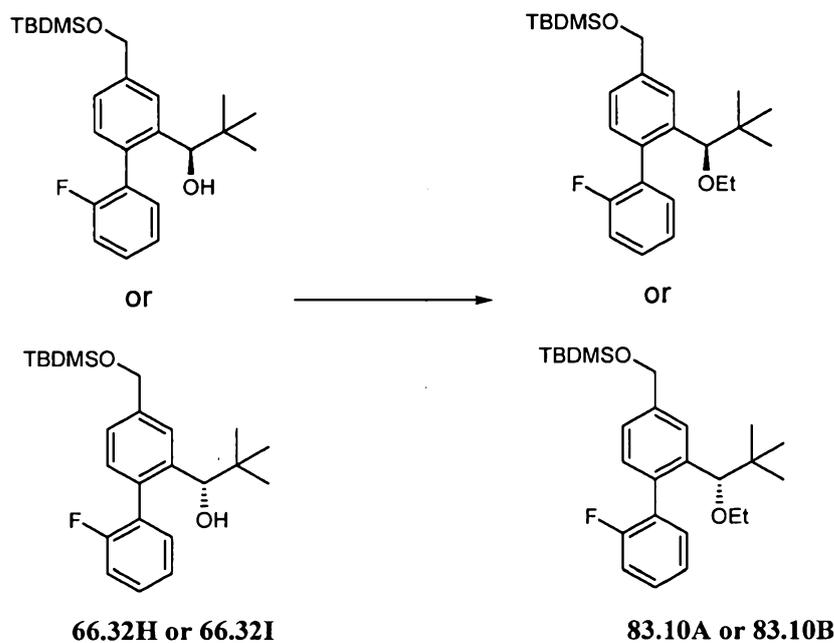
[01269] (3S)-3-Cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-5'-(methyloxy)-2-((1R)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-5'-(methyloxy)-2-((1S)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-5'-(methyloxy)-2-((1R)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-5'-(methyloxy)-2-((1S)-1,2,2-trimethylpropyl)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (83.6). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 66.18M or 66.18N derived from peak two from the chiral separation of 66.18I from the OD-column, described herein) to yield 83.6A or 83.6B (0.0253 g, 63% yield over the two steps). MS ESI (neg.) m/e: 521.2 (M-H)⁺.

[01270] (3S)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid (83.7). Example 83.7 was prepared using an alkylation and hydrolysis procedure similar to that used in Example 66.6 (using 83.B and 66.21J or 66.21K derived from peak two from the chiral separation of 66.21G from the OD-column, described herein) to yield 83.7A or 83.7B (0.0358 g, 78% yield over two steps). MS ESI (neg.) m/e: 547.3 (M-H)⁺.

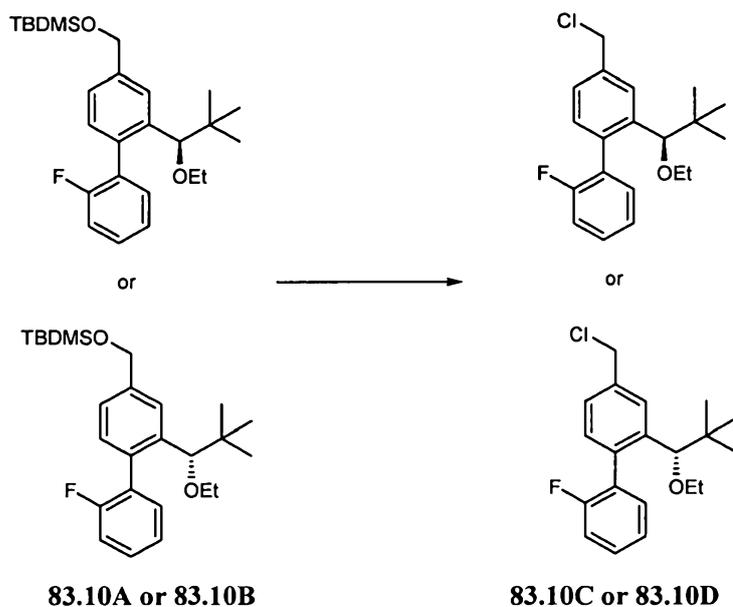
[01271] (3S)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid (83.8). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 83.B and 66.13H or 66.13I derived from peak two from the chiral separation of 66.13G from the OD-column, described herein) to yield 83.8A or 83.8B (0.0349 g, 62% yield over two steps). MS ESI (neg.) m/e: 537.3 (M-H)⁺.

[01272] (3S)-3-Cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1R)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1S)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1R)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1S)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (83.9). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 83.B and 66.30G or 66.30H derived from peak two from the chiral separation of 66.30D from the OD-column, described herein) to yield 83.8 (0.0256 g, 88% yield). MS ESI (neg.) m/e: 525.3 (M-H)⁺.

[01273] Example 83.10



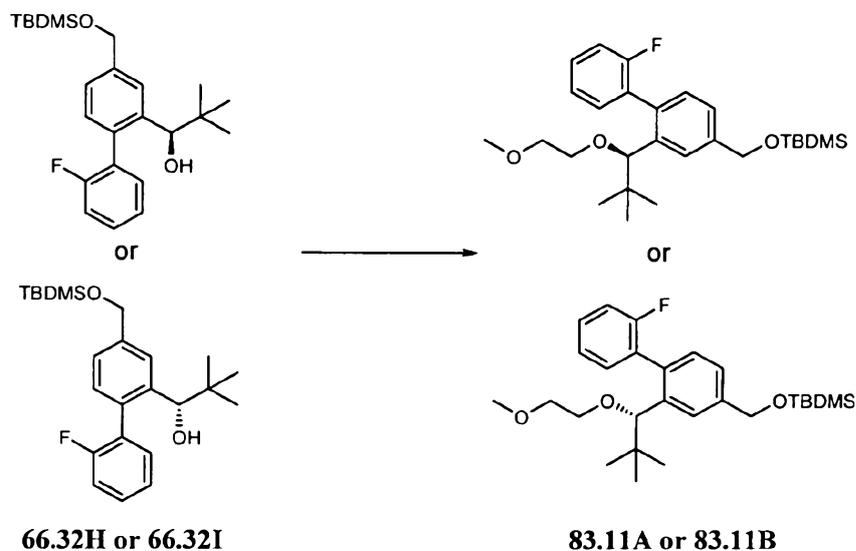
[01274] **(1,1-Dimethylethyl)((2-((1R)-1-(ethoxy)-2,2-dimethylpropyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)dimethylsilane or (1,1-dimethylethyl)((2-((1S)-1-(ethoxy)-2,2-dimethylpropyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)dimethylsilane (83.10 A or 83.10B).** To a stirred solution of **66.32H or 66.32I** (0.05 g, 0.1 mmol) in DMF (1 mL) at 23°C was added iodoethane (0.02 g, 0.1 mmol), followed by sodium hydride (0.004 g, 0.1 mmol). The reaction was then stirred at 60°C for 17 hours. Next, the reaction was diluted with water and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-5% EtOAc in hexanes) to yield **83.10A or 83.10B** as a colorless oil (0.042 g, 79% yield).



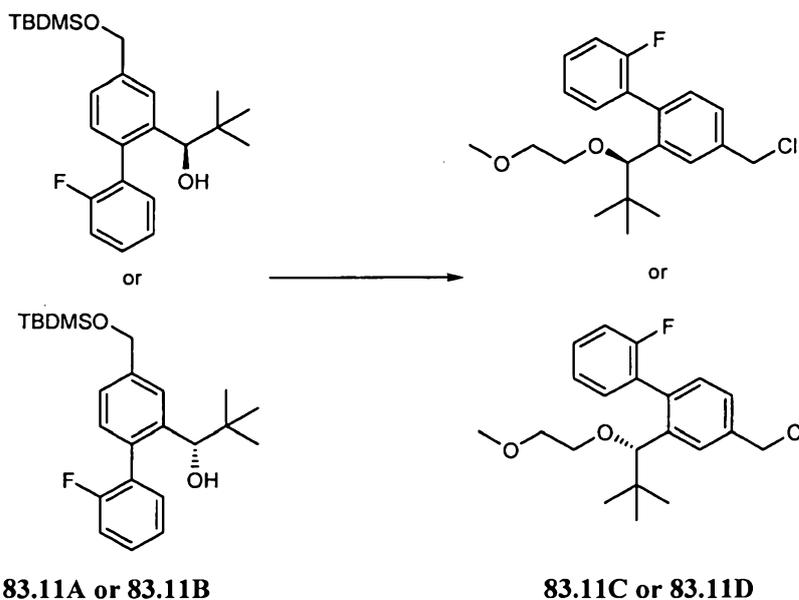
[01275] **4-(Chloromethyl)-2-((1R)-1-(ethyloxy)-2,2-dimethylpropyl)-2'-fluoro-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-1-(ethyloxy)-2,2-dimethylpropyl)-2'-fluoro-1,1'-biphenyl (83.10C or 83.10D).** To a stirred solution of **83.10A** or **83.10B** (0.042 g, 0.098 mmol) in DCM (0.98 mL, 0.098 mmol) and DMF (0.0076 mL) at 0°C was added thionyl chloride (0.014 mL, 0.20 mmol). The reaction was stirred at room temperature for one hour. Next, the reaction mixture was concentrated in vacuo. The product was then purified on silica gel (0-5% EtOAc in hexanes) to yield **83.10C** or **83.10D** as a colorless oil (0.029 g, 89% yield).

[01276] **(3S)-3-Cyclopropyl-3-(3-(((2-((1R)-1-(ethyloxy)-2,2-dimethylpropyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-1-(ethyloxy)-2,2-dimethylpropyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-1-(ethyloxy)-2,2-dimethylpropyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-1-(ethyloxy)-2,2-dimethylpropyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid (83.10).** The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using **83.B** and **83.10C** or **83.10D** derived from peak two from the chiral separation of **66.32E** from the OD-column, described herein) to yield **83.10** (0.0345 g, 79% yield over two steps). MS ESI (neg.) m/e: 521.2 (M-H)⁺.

[01277] **Example 83.11**

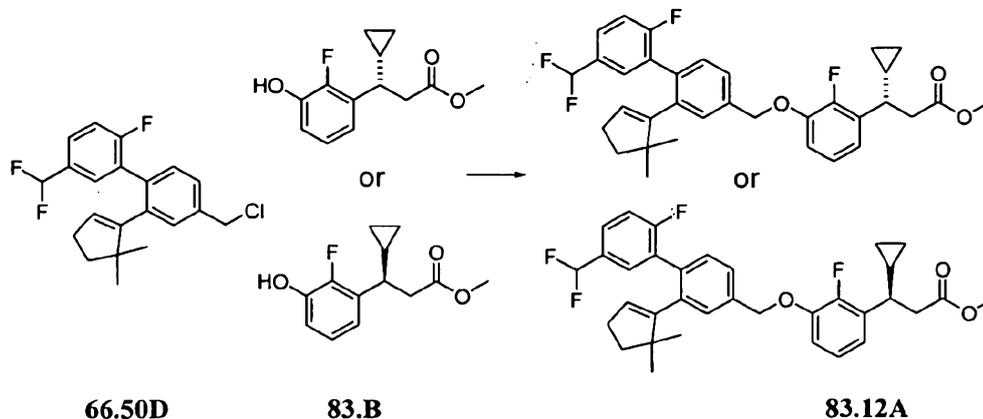


[01278] (1,1-Dimethylethyl)((2-((1R)-2,2-dimethyl-1-((2-(methoxy)ethyl)oxy)propyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)dimethylsilane or (1,1-dimethylethyl)((2-((1S)-2,2-dimethyl-1-((2-(methoxy)ethyl)oxy)propyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)dimethylsilane (**83.11A** or **83.11B**). To a stirred solution of **66.32H** or **66.32I** (0.05 g, 0.1 mmol) in DMF (1 mL) at 23°C was added 1-bromo-2-methoxyethane (0.02 g, 0.1 mmol)(commercially available from Aldrich) followed by sodium hydride (0.004 g, 0.1 mmol). The reaction was stirred at 60°C for 17 hours. Next, the reaction was diluted with water and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-5% EtOAc in hexanes) to yield **83.11A** or **83.11B** as a colorless oil (0.046g, 92%).

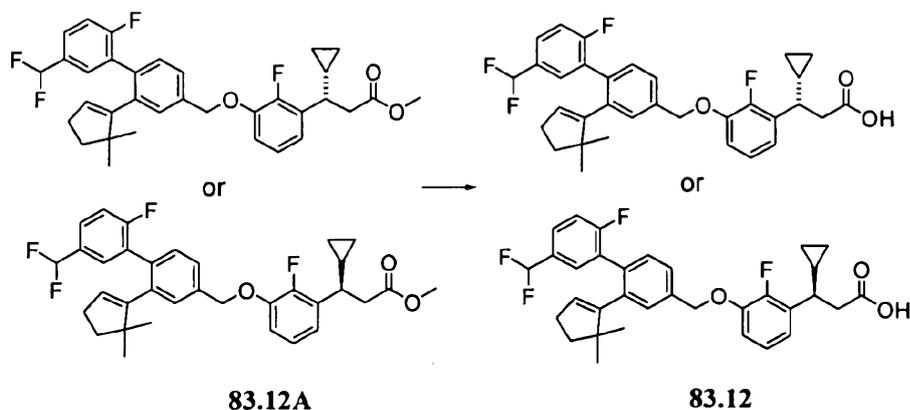


[01279] **4-(Chloromethyl)-2-((1R)-2,2-dimethyl-1-((2-(methoxy)ethyl)oxy)propyl)-2'-fluoro-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-2,2-dimethyl-1-((2-(methoxy)ethyl)oxy)propyl)-2'-fluoro-1,1'-biphenyl (83.11C or 83.11D).** To a stirred solution of **83.11A or 83.11B** (0.046 g, 0.100 mmol) in DCM (1.00 mL) and DMF (0.0077 mL) at 0°C was added thionyl chloride (0.015 mL, 0.20 mmol). The reaction was stirred at room temperature for one hour. Next, the reaction was concentrated in vacuo. The product was then purified on silica gel (0-5% EtOAc in hexanes) to yield **83.11C or 83.11D** as a colorless oil (0.033 g, 91% yield)

[01280] **(3S)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-((2-(methoxy)ethyl)oxy)propyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-((2-(methoxy)ethyl)oxy)propyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-((2-(methoxy)ethyl)oxy)propyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-((2-(methoxy)ethyl)oxy)propyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid (83.11).** The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using **83.B** and **83.11C or 83.11D** derived from peak two from the chiral separation of **66.32E** from the OD-column, described herein) to yield **83.11E or 83.11F** (0.0287 g, 54% yield over two steps). MS ESI (neg.) m/e: 551.2 (M-H)⁺.

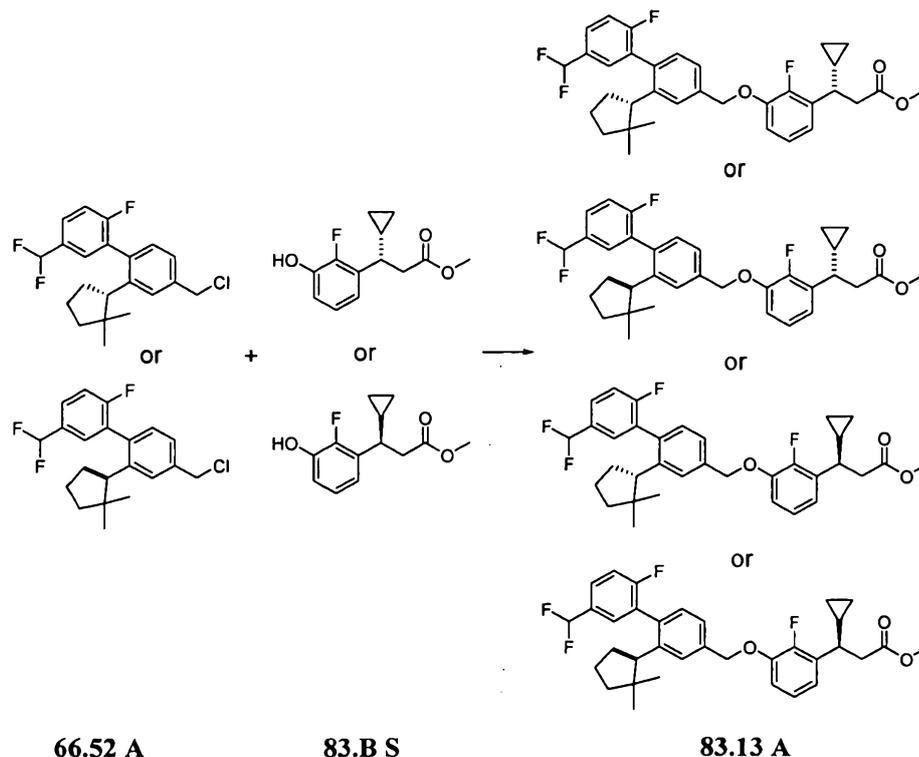
[01281] Example 83.12

[01282] Methyl (3S)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoate (83.12A). To a vial containing **83.B** (0.0322 g, 0.135 mmol) in 1.00 mL dry DMF was added cesium carbonate (0.0568 g, 0.174 mmol). The mixture was stirred at room temperature for 10 minutes, and then **66.50D** (0.0551 g, 0.151 mmol) was added. After 22 hours, the reaction was diluted with water and then extracted five times with EtOAc. The combined organic layers were then washed one time with brine and dried over anhydrous magnesium sulfate. The solid was filtered off, and the solvent was concentrated. The residue was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to afford **83.12A** (62.5 mg, 82% yield). MS ESI (pos.) m/e: 583.9 (M+H₂O)⁺.

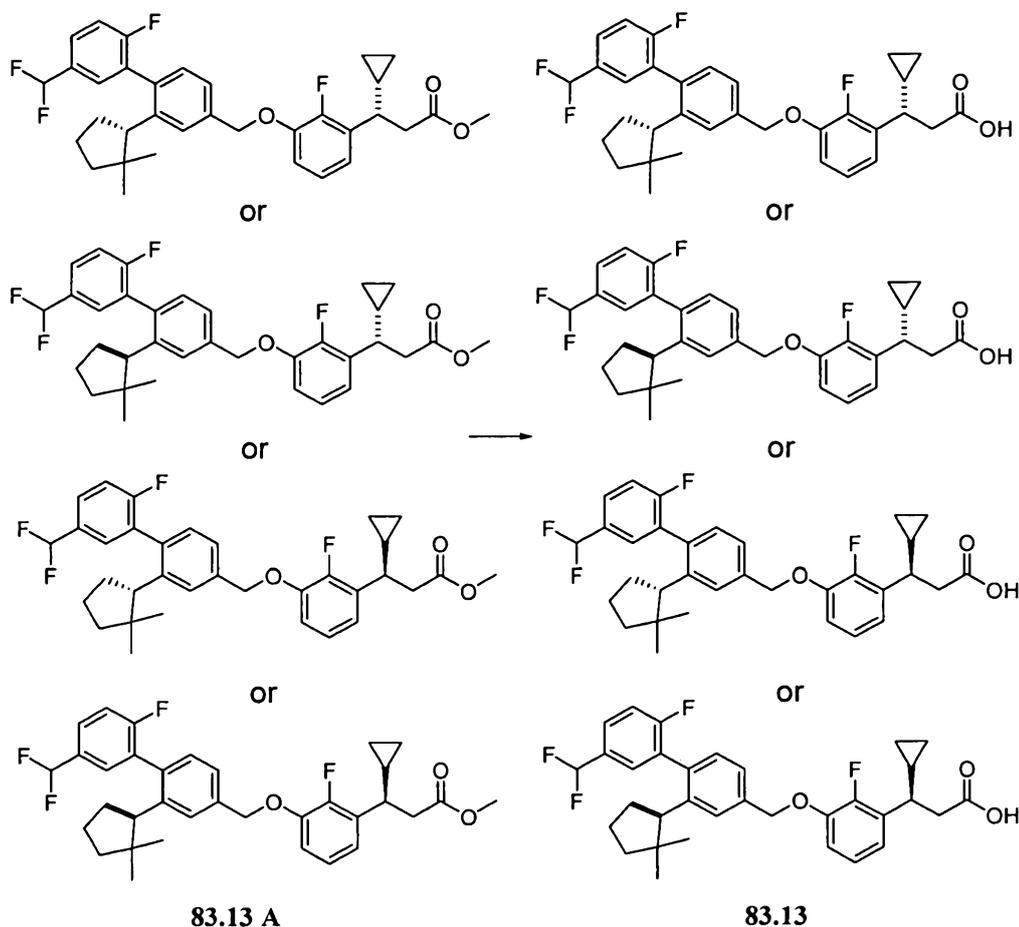


[01283] (3S)-3-Cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid (**83.12**). A pre-mixed solution of 2M NaOH (0.5 mL, 1.00 mmol), THF (1 mL), and MeOH (1 mL) was added to a vial containing **83.12A** (0.0625 g, 0.110 mmol). This solution was stirred at room temperature and monitored with TLC and LC-MS. After 24 hours, the mixture was diluted with water and acidified with 1 M aqueous HCl solution, and then extracted five times with EtOAc. The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel flash chromatography (0-40% EtOAc/hexane) to afford **83.12** (45.2 mg, 74% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.44 (3 H, td, J=6.8, 1.2 Hz), 7.36 (2 H, m), 7.14 (1 H, t, J=9.0 Hz), 7.05 (1 H, m), 6.96 (2 H, m), 6.76 (1H, t), 5.50 (1 H, s), 5.17 (2 H, s), 2.86 (2 H, d, J=7.4 Hz), 2.69 (1 H, ddd, J=10.0, 7.4, 7.2 Hz), 2.23 (2 H, td, J=7.0, 2.3 Hz), 1.64 (2 H, t, J=7.0 Hz), 1.22 (1 H, m), 0.84 (6 H, s), 0.65 (1 H, m), 0.46 (1 H, m), 0.33 (1 H, dq, J=9.6, 4.8 Hz), 0.20 (1 H, dq, J=9.6, 4.9 Hz). MS ESI (neg.) m/e: 550.9 (M-H)⁺.

[01284] **Example 83.13**



[01285] Methyl (3S)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoate or methyl (3S)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoate (83.13 A). To a vial containing 83.B (0.0371 g, 0.156 mmol) in 1.00 mL dry DMF was added cesium carbonate (0.0622 g, 0.191 mmol). The mixture was stirred at room temperature for 10 minutes, and then 66.52A (0.0623 g, 0.170 mmol) was added. After 22 hours, the reaction was diluted with water and then extracted five times with EtOAc. The combined organic layers were then washed one time with brine and dried over anhydrous magnesium sulfate. The solid was filtered off, and the solvent was concentrated. The residue was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to afford 83.13 A (78.5 mg, 89% yield). MS ESI (pos.) m/e: 586.0 (M+H₂O)⁺.



[01286] (3S)-3-Cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((5'-(difluoromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid (83.13). A pre-mixed solution of 2M NaOH (0.5 mL, 1.00 mmol), THF (1 mL), and MeOH (1 mL) was added to a vial containing 83.13A (0.0785 g, 0.138 mmol). This solution was stirred at room temperature and monitored with TLC and LC-MS. After 24 hours, the mixture was diluted with water and acidified with 1M aqueous HCl solution and then extracted five times with EtOAc. The organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was

purified with reverse phase HPLC using 30-90% Solvent B (0.1% TFA in acetonitrile) over 45 minutes to afford **83.13** that was lyophilized (39.6 mg, 52% yield). MS ESI (neg.) m/e: 553.0 (M-H)⁺.

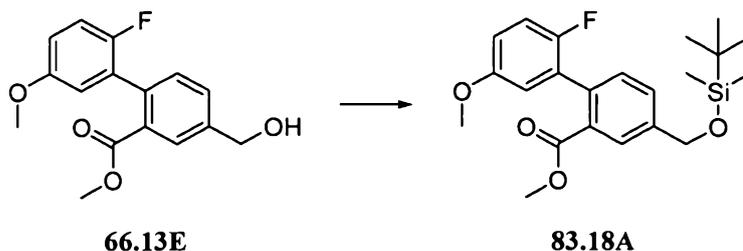
[01287] (3S)-3-Cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid (**83.14**). MS ESI (pos.) m/e: 550.3 (M+H₂O)⁺, 555.3 (M+Na)⁺.

[01288] (3S)-3-Cyclopropyl-3-(3-(((2-(2,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-(2,2-dimethylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid (**83.15**). MS ESI (pos.) m/e: 526.3 (M+H₂O)⁺, 531.2 (M+Na)⁺.

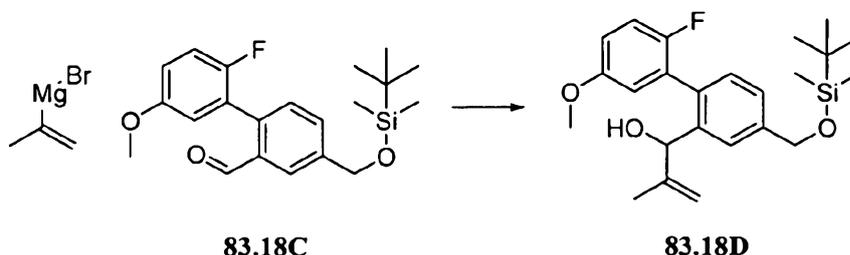
[01289] (3S)-3-Cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid (**83.16**). MS ESI (pos.) m/e: 568.3 (M+H₂O)⁺, 573.3 (M+Na)⁺.

[01290] (3S)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid (**83.17**). MS ESI (neg.) m/e: 533.2 (M-H)⁺.

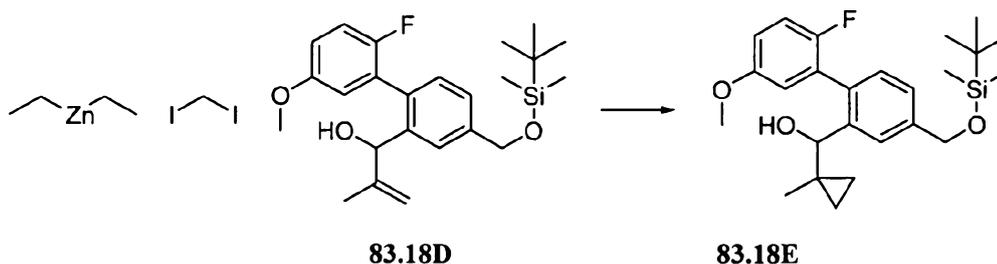
[01291] **Example 83.18**



purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **83.18C** (1.05 g, 87% yield) as a colorless oil.

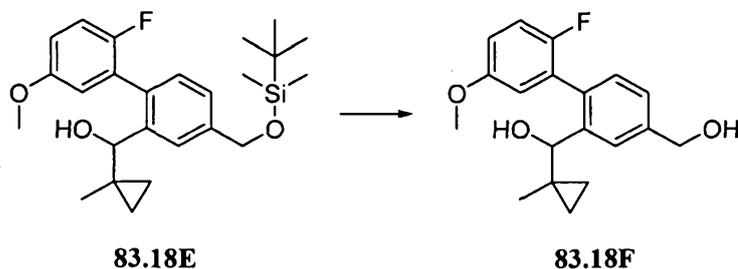


[01295] **1-(4-(((1,1-Dimethylethyl)(dimethyl)silyl)oxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)-2-methyl-2-propen-1-ol (83.18D)**. A 250 mL round bottom flask was charged with **83.18C** (1.05 g, 2.80 mmol) and THF (15 mL) and cooled to -78°C under N₂. To the cold solution was added isopropenylmagnesium bromide (0.5 M in THF) (available from Aldrich) (11.2 mL, 5.61 mmol) dropwise. The mixture was stirred for 30 minutes at -78°C. The cooling bath was removed, and the mixture was stirred for 30 minutes at ambient temperature. The reaction was quenched with saturated aqueous NH₄Cl and diluted with EtOAc. The organic phase was washed with water and brine, dried (MgSO₄), and concentrated. The residue was purified by silica gel flash chromatography (0-15% EtOAc/hexane) to afford **83.18D** (1.05 g, 90% yield) as a colorless oil.

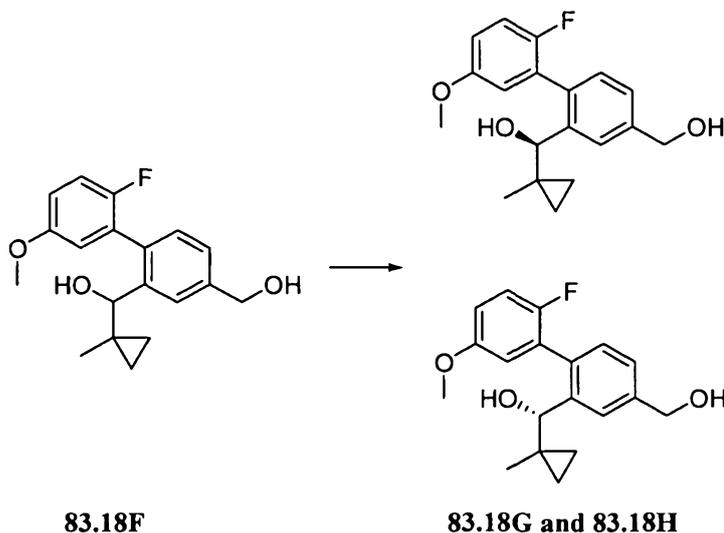


[01296] **(4-(((1,1-Dimethylethyl)(dimethyl)silyl)oxy)methyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-2-yl)(1-methylcyclopropyl)methanol (83.18E)**. A 100 mL round bottom flask was charged with **83.18D** (0.92 g, 2.2 mmol), DCM (22 mL), and diiodomethane (available from Aldrich) (0.27 mL, 3.3 mmol) and cooled to 0 °C under N₂. To the cold solution was added diethylzinc (1.0 M in heptane) (available from Aldrich) (3.3 mL, 3.3 mmol) at a rapid drip. The colorless mixture was stirred for 5 minutes. The cooling bath was removed, and the mixture was stirred for 2 hours at ambient temperature. The reaction was quenched with saturated aqueous NH₄Cl and diluted with EtOAc. The organic phase was washed with 1 M Na₂S₂O₃ and brine, dried

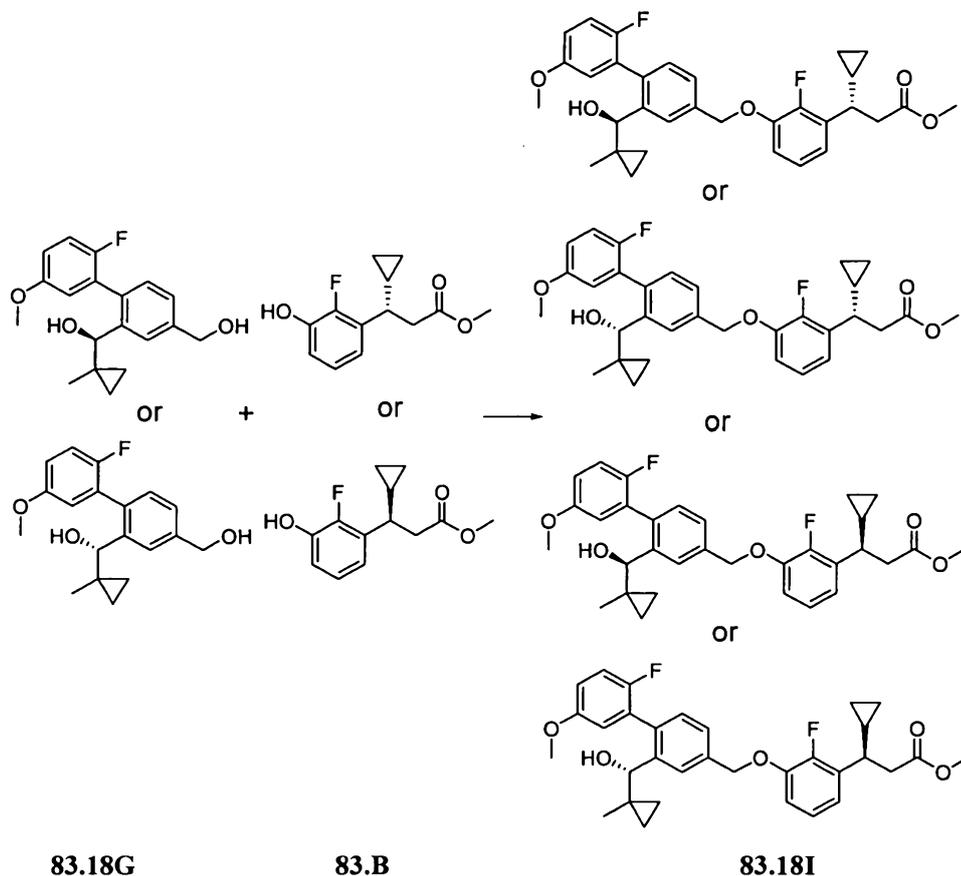
(MgSO₄), and concentrated. The residue was purified by silica gel flash chromatography (0-15% EtOAc/hexane) to afford **83.18E** (0.81 g, 85%) as a colorless oil.



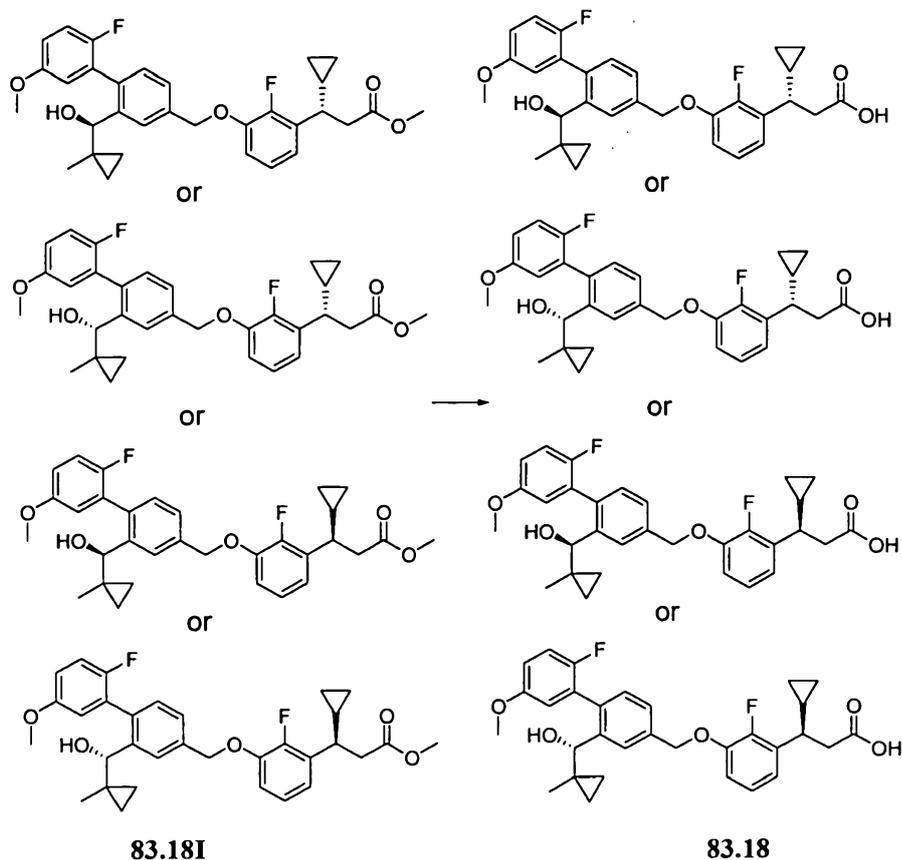
[01297] **(2'-Fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)(1-methylcyclopropyl)methanol (83.18F)**. A 200 mL round bottom flask was charged with **83.18E** (0.80 g, 1.9 mmol), MeOH (10 mL), and PPTS (0.047 g, 0.19 mmol). The solution was stirred overnight at room temperature and diluted with EtOAc. The organic phase was washed with water and brine, dried (MgSO₄), and concentrated. The crude product was purified by silica gel flash chromatography (20-55% EtOAc/hexane) to afford **83.18F** (0.52 g, 88%) as a colorless oil.



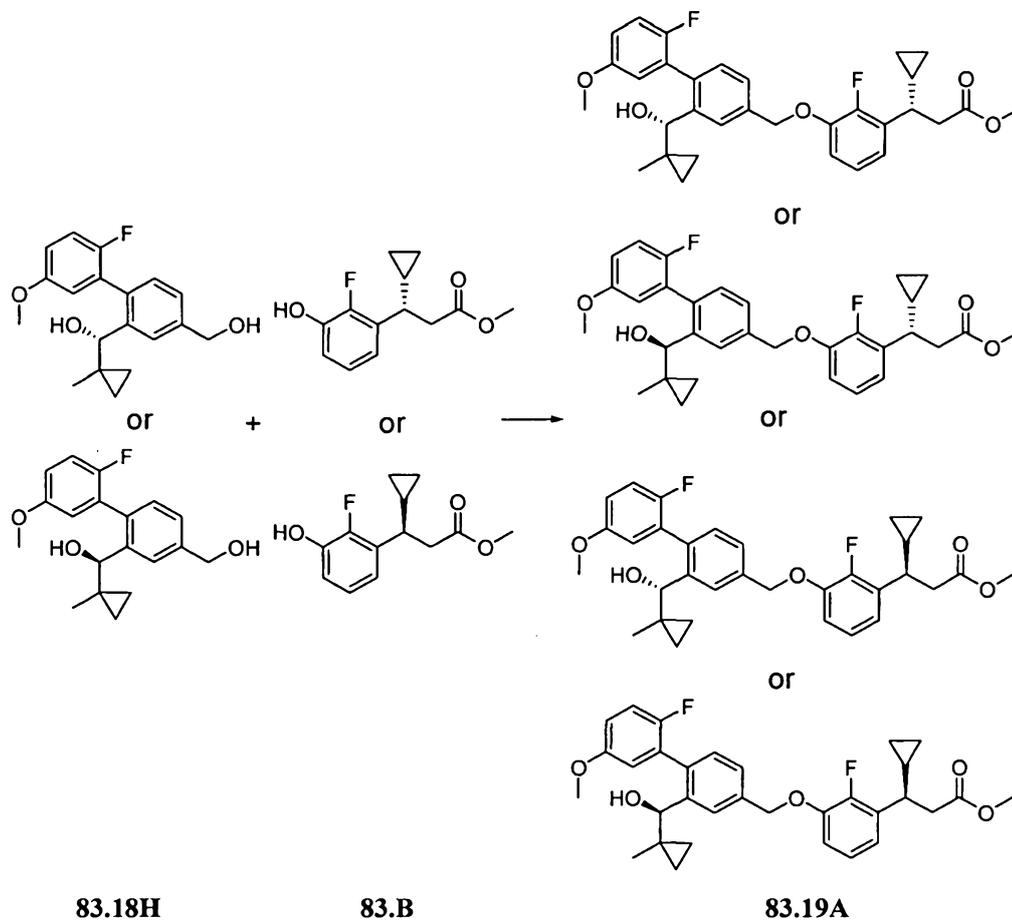
[01298] **(R)-(2'-Fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)(1-methylcyclopropyl)methanol and (S)-(2'-fluoro-4-(hydroxymethyl)-5'-(methoxy)-1,1'-biphenyl-2-yl)(1-methylcyclopropyl)methanol (83.18G and 83.18H)**. Racemic **83.18F** (0.52 g, 1.6 mmol) was resolved by chiral HPLC (Chiralcel OD column, 5% IPA/hexane, detection at 220 nm) to afford (in order of elution) **83.18G** (0.23 g, 88% yield, 99% e.e.) and **83.18H** (0.23 g, 88% yield, 99% e.e.) as colorless oils.



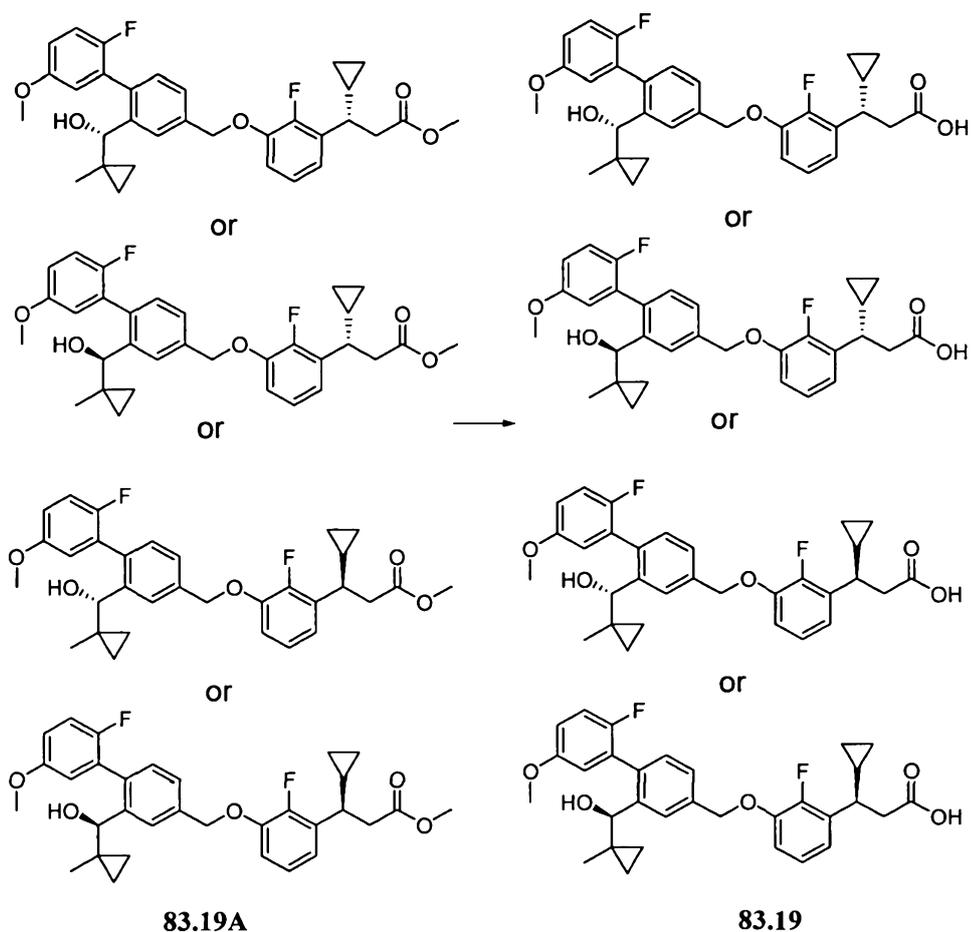
[01299] **Methyl (3S)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((R)-hydroxy(1-methylcyclopropyl)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3S)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((S)-hydroxy(1-methylcyclopropyl)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((R)-hydroxy(1-methylcyclopropyl)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((S)-hydroxy(1-methylcyclopropyl)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (83.18I).** A screw-cap vial was charged with **83.B** (0.075 g, 0.31 mmol), **83.18G** (0.100 g, 0.31 mmol), triphenylphosphine (0.12 g, 0.47 mmol), and THF (1.8 mL). To the solution was added diethyl azodicarboxylate (0.075 mL, 0.47 mmol) dropwise at room temperature. The mixture was stirred for 1 hour, diluted with brine, and extracted with EtOAc. The combined organic layers were dried (MgSO_4) and concentrated. The residue was purified by silica gel flash chromatography (0-25% EtOAc/hexane) to afford **83.18I** (0.122 g, 72% yield) as a colorless oil.



[01300] (3S)-3-Cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1R)-hydroxy(1-methylcyclopropyl)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1S)-hydroxy(1-methylcyclopropyl)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1R)-hydroxy(1-methylcyclopropyl)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1S)-hydroxy(1-methylcyclopropyl)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (**83.18**). A screw-cap vial was charged with **83.18I** (0.021 g, 0.039 mmol), 2:1 THF/MeOH (1.5 mL), and 1 N LiOH (0.50 mL, 0.50 mmol). The mixture was stirred overnight at room temperature, concentrated, quenched with a slight excess of 1 N HCl, and extracted with EtOAc. The combined organic layers were dried (MgSO₄) and concentrated. The residue was purified by silica gel flash chromatography (0-40% EtOAc/hexane) to afford **83.18** (0.0184 g, 90% yield) as a white solid. MS ESI (neg.) m/e: 521.2 (M-H)⁺.

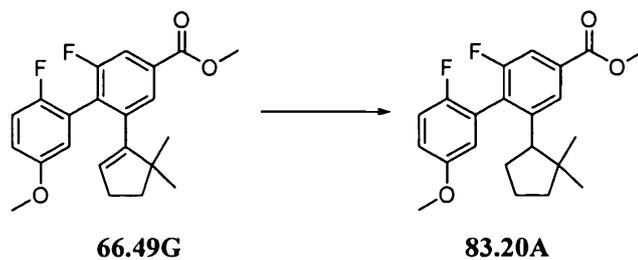
[01301] Example 83.19

[01302] Methyl (3S)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((S)-hydroxy(1-methylcyclopropyl)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3S)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((R)-hydroxy(1-methylcyclopropyl)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((S)-hydroxy(1-methylcyclopropyl)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((R)-hydroxy(1-methylcyclopropyl)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (83.19A). 83.19A was prepared from 83.18H and 83.B according to the analogous method described in Example 83.18.

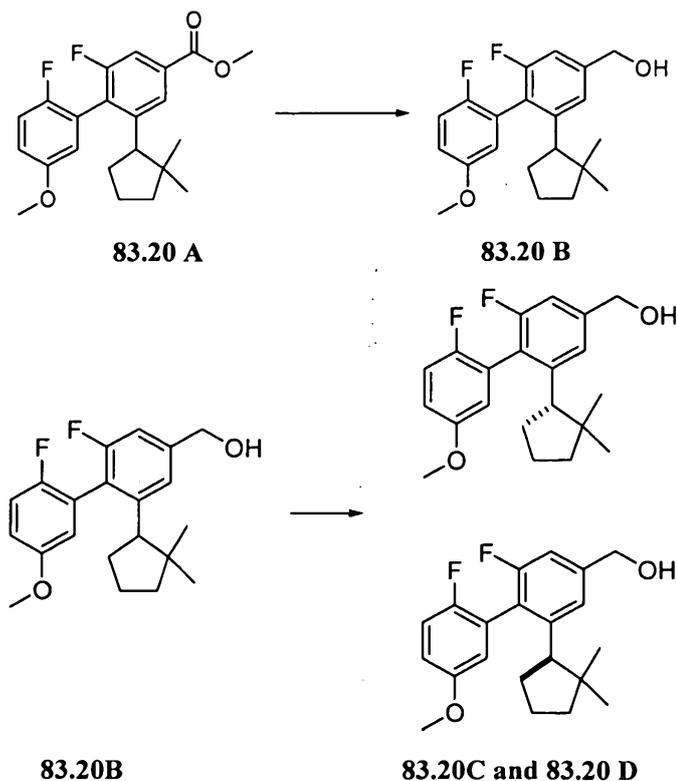


[01303] (3S)-3-Cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1S)-hydroxy(1-methylcyclopropyl)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1R)-hydroxy(1-methylcyclopropyl)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1S)-hydroxy(1-methylcyclopropyl)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1R)-hydroxy(1-methylcyclopropyl)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (83.19). 83.19 was prepared from 83.19A according to the analogous method described in Example 83.18. MS ESI (neg.) m/e: 521.2 (M-H)⁺.

[01304] **Example 83.20**

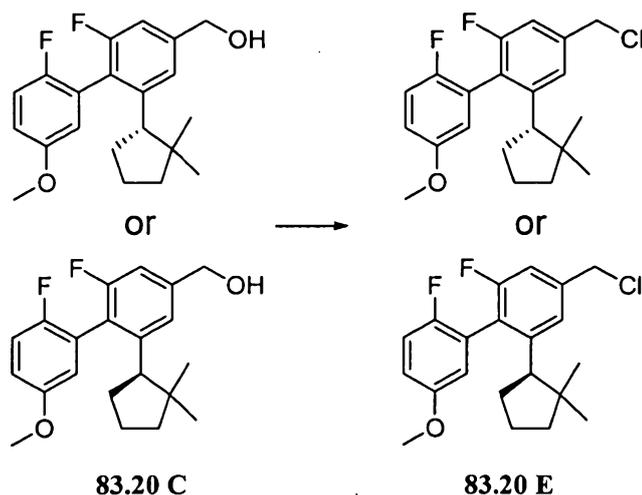


[01305] Methyl 2-(2,2-dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (83.20A). To a flask containing **66.49 G** (0.7168 g, 1.925 mmol) in dry MeOH (8 mL) and EtOAc (5 mL) was added palladium (10wt. % on activated carbon)(0.2103 g, 0.1976 mmol). After purging, the mixture was stirred under an atmosphere of hydrogen at room temperature. After 18.5 hours, the mixture was filtered through Celite. After concentration, the residue was identified **83.20A** (703.6 mg, 98% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.88 (1 H, s), 7.65 (1 H, dd, J=9.4, 1.6 Hz), 7.13 (2 H, m), 6.96 (2 H, m), 6.77 (1 H, dd, J=5.5, 3.1 Hz), 3.95 (3 H, s), 3.80 (3 H, s), 2.76 (1 H, ddd, J=10.3, 8.3, 1.8 Hz), 2.19 (1 H, m), 2.08 (1 H, m), 1.91 (1 H, m), 1.75 (2 H, m), 1.45 (1 H, m), 0.78 (3 H, s), 0.64 (3 H, s).



[01306] (2-(2,2-Dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-

biphenyl-4-yl)methanol (83.20B). To a cooled solution of **83.20A** (0.7036 g, 1.879 mmol) in dry THF (15 mL) at 0°C was added LAH (1.0 M in THF)(4 mL, 4.0 mmol) dropwise. Upon complete addition, the reaction was maintained at 0°C and was monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction. Gas evolution occurred. The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified by flash chromatography (SiO₂ gel 60, eluted with 0%-50% EtOAc in hexanes). Fractions containing the desired product were combined and concentrated to provide a colorless oil that solidified as **83.20B** (300.5 mg, 46 % yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.16 (1 H, s), 7.10 (2 H, m), 6.92 (1 H, m), 6.77 (1 H, dd, J=5.9, 3.1 Hz), 4.74 (2 H, s), 3.81 (3 H, m), 2.73 (1 H, ddd, J=10.3, 8.3, 1.8 Hz), 2.17 (1 H, m), 2.04 (1 H, m), 1.87 (1 H, m), 1.73 (3 H, m), 1.42 (1 H, m), 0.78 (3 H, s), 0.64 (3 H, s). Chiral separation of **83.20B** was accomplished on Chiracel-OJ (2% IPA in hexane) to provide **83.20C** (peak 1) and **83.20D** (peak 2). Both enantiomers were used to synthesize example compounds, and both enantiomers gave active compounds.

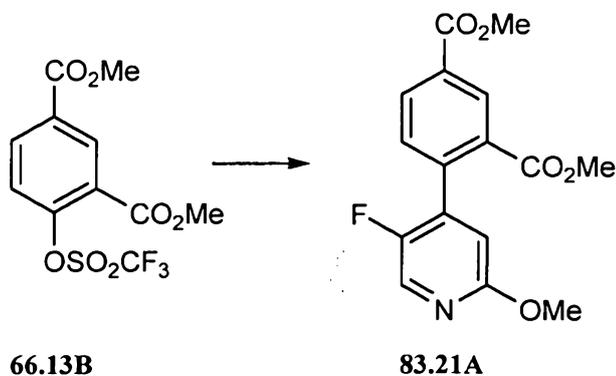


[01307] 4-(Chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl (83.20E). To a solution of **83.20C** (0.1171 g, 0.338 mmol) in dry DCM (4.5 mL) and dry DMF (0.03 mL) was added thionyl chloride (0.05 mL, 0.685 mmol) at 0 °C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 19 hours, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **83.20E**

(99.7 mg, 81% yield). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 7.18 (1 H, d, $J=1.6$ Hz), 7.13 (2 H, m), 6.95 (1 H, m), 6.77 (1 H, dd, $J=5.9, 3.1$ Hz), 4.68 (2 H, m), 3.84 (3 H, m), 2.73 (1 H, ddd, $J=10.3, 8.3, 1.8$ Hz), 2.18 (1 H, m), 2.01 (1 H, m), 1.88 (1 H, m), 1.73 (3 H, m), 1.44 (1 H, m), 0.78 (3 H, s), 0.64 (3 H, s).

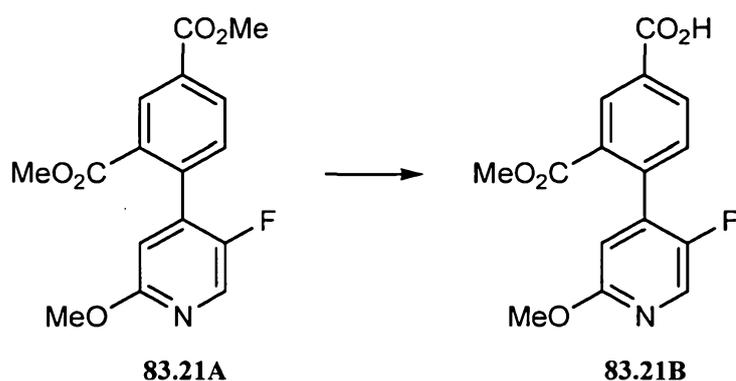
[01308] (3S)-3-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid (**83.20**). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using **83.B** and **83.20E** derived from peak one from the chiral separation of the racemic alcohol **83.20C** on the OJ column, described herein) to yield **83.20** (42.5 mg, 92% yield). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 7.23 (1 H, d, $J=0.8$ Hz), 7.17 (3 H, m), 6.94 (3 H, m), 6.78 (1 H, dd, $J=5.9, 3.1$ Hz), 5.19 (2 H, m), 3.79 (3 H, s), 2.86 (2 H, d, $J=7.4$ Hz), 2.79 (2 H, m), 2.18 (1 H, m), 2.02 (1 H, m), 1.86 (1 H, m), 1.72 (1 H, m), 1.53 (1 H, ddd, $J=12.7, 8.2, 4.9$ Hz), 1.42 (2 H, m), 1.20 (1 H, m), 0.73 (3 H, s), 0.67 (4 H, m), 0.48 (1 H, m), 0.34 (1 H, dq, $J=9.6, 4.9$ Hz), 0.25 (1 H, m). MS ESI (neg.) m/e : 551.2 (M-H) $^+$.

[01309] Example 83.21

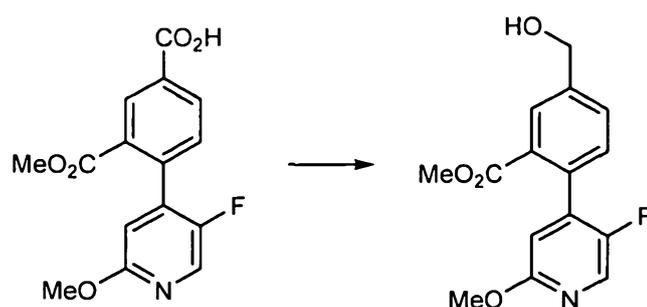


[01310] **Dimethyl 4-(5-fluoro-2-(methoxy)-4-pyridinyl)-1,3-benzenedicarboxylate (83.21A)**. To a stirred solution of **66.13B** (1.00 g, 2.9 mmol) in DMF (12 mL) at 23°C was added 5-fluoro-2-methoxypyridin-4-ylboronic acid (0.75 g,

4.4 mmol)(commercially available from Asymchem), potassium carbonate (1.2 g, 8.8 mmol), followed by tetrakis(triphenylphosphine)palladium (0.24 g, 0.20 mmol). The mixture was heated to 90°C. The reaction mixture was then stirred for 17 hours and then cooled to room temperature. The reaction was diluted with brine and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-30% EtOAc in hexanes) to yield **83.21A** as a colorless solid (0.860 g, 92% yield).

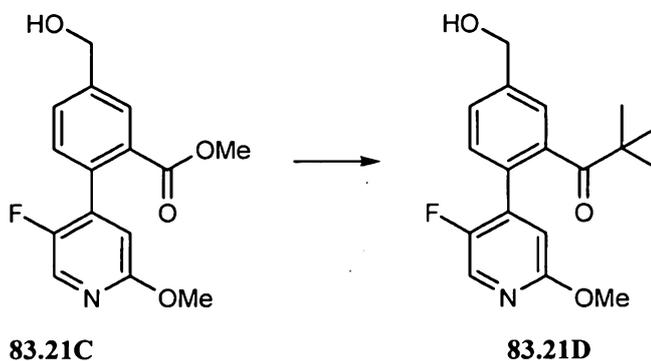


[01311] **4-(5-Fluoro-2-(methoxy)-4-pyridinyl)-3-((methoxy)carbonyl)benzoic acid (83.21B)**. To a stirred solution of **83.21A** (0.860 g, 2.7 mmol) in THF (7.00 mL) and MeOH (7.00 mL) at 0°C was added potassium hydroxide (1.5 mL, 3.0 mmol) slowly to maintain the temperature below 6°C. The reaction mixture was allowed to warm to room temperature and stirred for 17 hours. After which, the reaction was acidified with 1N HCl and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure to yield **83.21B** as a colorless solid (0.82 g, 100% yield).

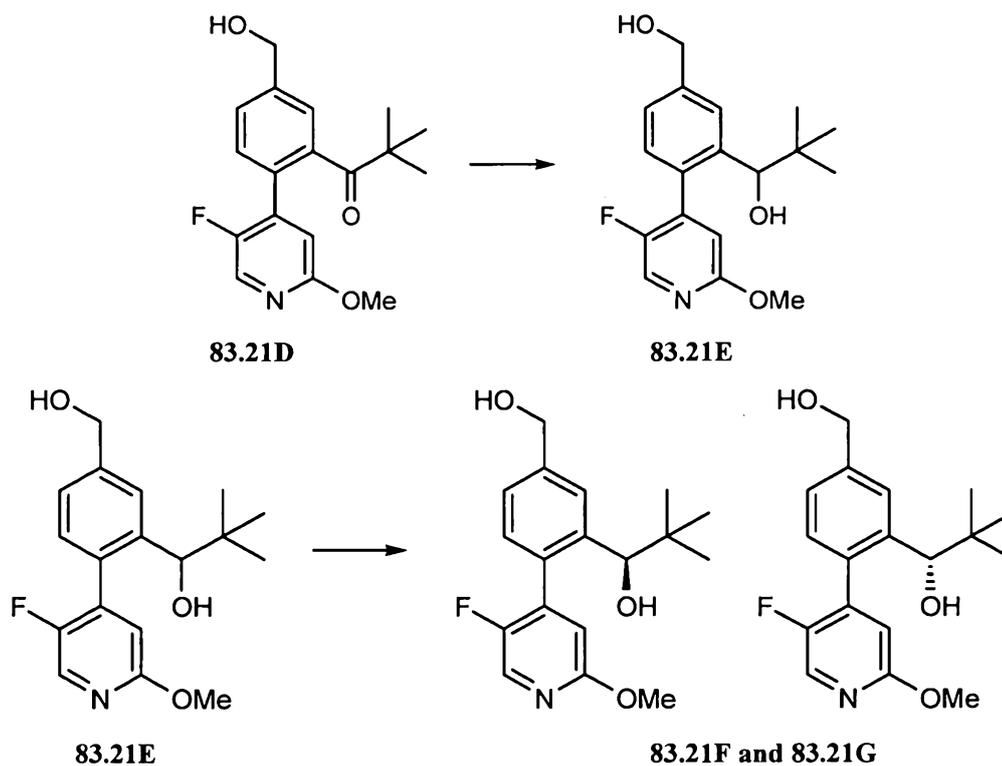


83.21B**83.21C**

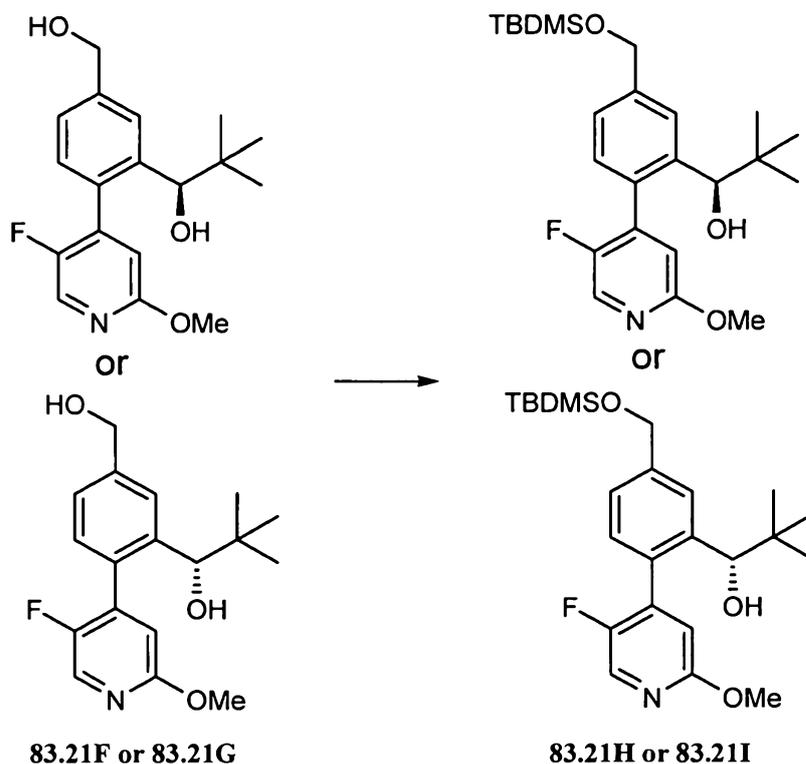
[01312] **Methyl 2-(5-fluoro-2-(methoxy)-4-pyridinyl)-5-(hydroxymethyl)benzoate (83.21C)**. To a stirred solution of 4-(5-fluoro-2-methoxypyridin-4-yl)-3-(methoxycarbonyl)benzoic acid **83.21B** (0.416 g, 1 mmol) in THF (14 mL) at 0°C was added borane-THF (3 mL, 3 mmol, 1.0M). The reaction was warmed to 23°C and stirred for 46 hours. The reaction was then concentrated in vacuo. The reaction was diluted with 1N HCl and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-40% EtOAc in hexanes) to yield **83.21C** as a colorless solid (0.307 g, 77% yield).



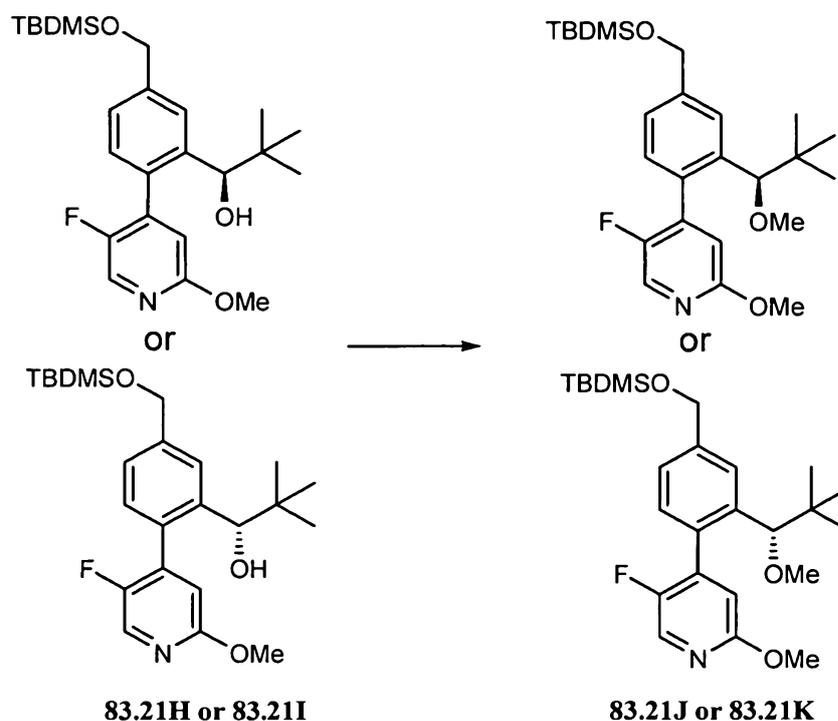
[01313] **1-(2-(5-Fluoro-2-(methoxy)-4-pyridinyl)-5-(hydroxymethyl)phenyl)-2,2-dimethyl-1-propanone (83.21D)**. To a stirred solution of methyl 2-(5-fluoro-2-methoxypyridin-4-yl)-5-(hydroxymethyl)benzoate **83.21C** (0.307 g, 1 mmol) in THF (11 mL) at -78°C was added tert-butyl lithium (2 mL, 3 mmol). The reaction mixture was stirred for one hour and then quenched with a saturated solution of ammonium chloride and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-40% EtOAc in hexanes) to yield **83.21D** as a colorless solid (0.28 g, 84% yield).



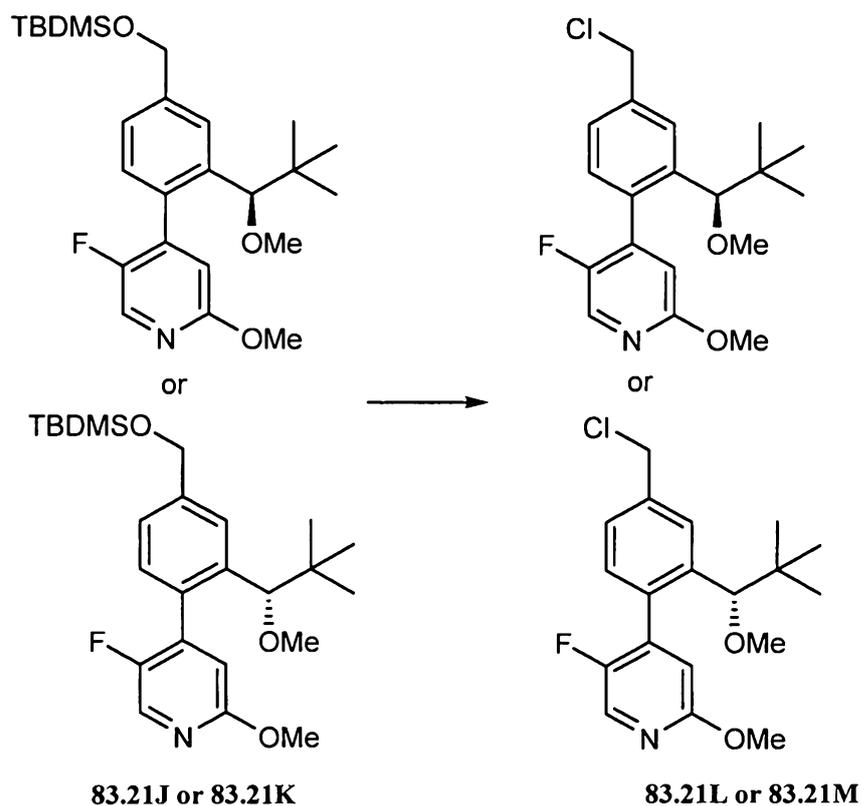
[01314] (1R)-1-(2-(5-Fluoro-2-methoxyphenyl)-5-(hydroxymethyl)phenyl)-2,2-dimethylpropan-1-ol or (1S)-1-(2-(5-fluoro-2-methoxyphenyl)-5-(hydroxymethyl)phenyl)-2,2-dimethylpropan-1-ol (**83.21F** or **83.21G**). To a stirred solution of 1-(2-(5-fluoro-2-methoxyphenyl)-5-(hydroxymethyl)phenyl)-2,2-dimethylpropan-1-one **83.21D** (0.130 g, 0.4 mmol) in THF (2 mL) at 0°C was added LAH (0.6 mL, 0.6 mmol, 1.0M). The reaction was stirred for 3 hours. 1N NaOH(aq) was then added to quench the reaction mixture. The reaction was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **83.21F** and **83.21G** as a colorless solid (0.120 g, 92% yield). Chiral separation of **83.21E** was accomplished on Chiracel-OD (4%IPA in hexane) to provide **83.21F** (peak one-23.87 mins) and **83.21G** (peak two-29.04 mins). Both enantiomers were used to synthesize example compounds, and both enantiomers gave active example compounds. However, the enantiomer corresponding to peak 2 provided the most active example compounds. ¹



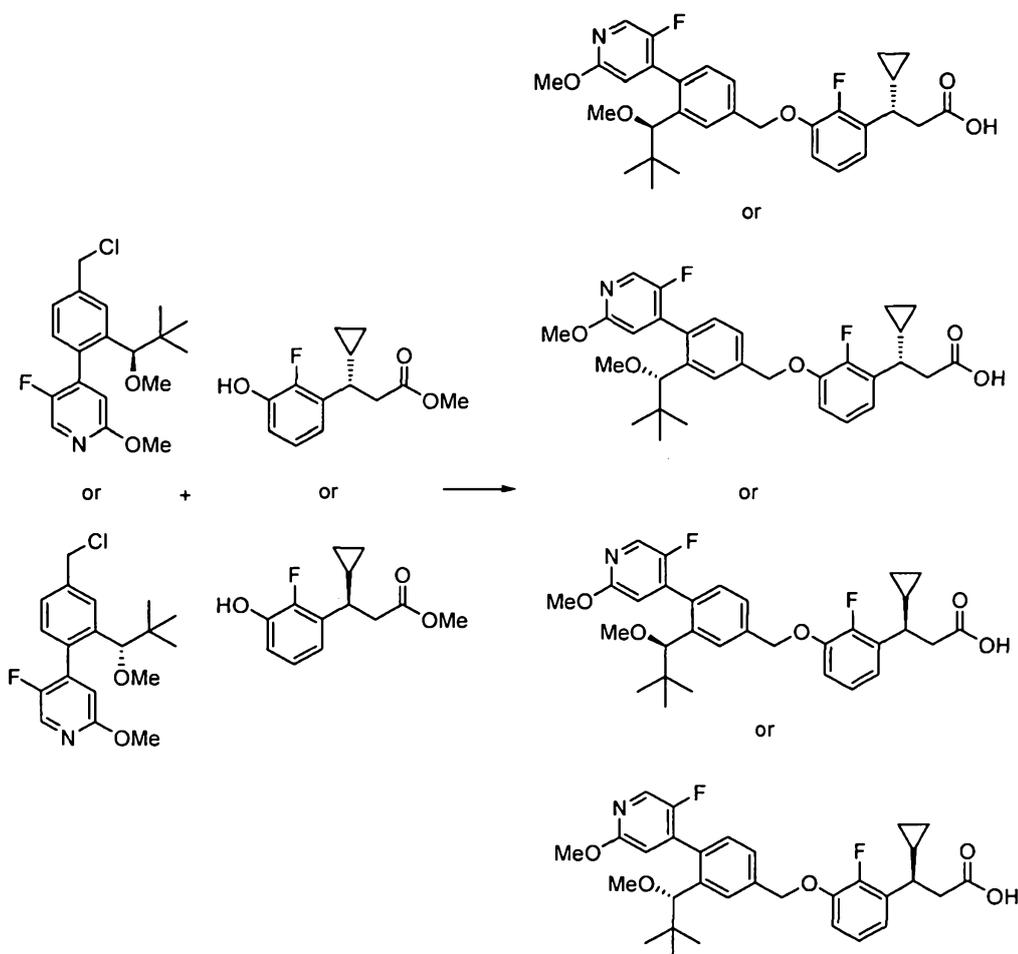
[01315] **(1R)-1-(5-(((1,1-Dimethylethyl)(dimethyl)silyl)oxy)methyl)-2-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)-2,2-dimethyl-1-propanol or (1S)-1-(5-(((1,1-dimethylethyl)(dimethyl)silyl)oxy)methyl)-2-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)-2,2-dimethyl-1-propanol (83.21H or 83.21I.)** To a stirred solution of **83.21F or 83.21G** (0.050 g, 0.2 mmol) in DCM (2 mL) at 23°C was added tert-butyldimethylsilyl chloride (0.03 mL, 0.2 mmol), followed by TEA (0.03 mL, 0.2 mmol) and DMAP (0.002 g, 0.02 mmol). The reaction was then stirred for 24 hours and then concentrated in vacuo. The reaction was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **83.21H or 83.21I** as a colorless oil (0.062 g, 91% yield).



[01316] 4-(4-(((1,1-Dimethylethyl)(dimethyl)silyl)oxy)methyl)-2-((1R)-2,2-dimethyl-1-(methoxy)propyl)phenyl)-5-fluoro-2-(methoxy)pyridine or 4-(4-(((1,1-dimethylethyl)(dimethyl)silyl)oxy)methyl)-2-((1S)-2,2-dimethyl-1-(methoxy)propyl)phenyl)-5-fluoro-2-(methoxy)pyridine (83.21J or 83.21K.) To a stirred solution of **83.21H** or **83.21I** (0.062 g, 0.14 mmol) in DMF (1.4 mL) at 23°C was added iodomethane (0.018 mL, 0.29 mmol), followed by sodium hydride (0.0069 g, 0.29 mmol). The reaction was then stirred at 50°C for 15 hours, diluted with water and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-40% EtOAc in hexanes) to yield **83.21J** or **83.21K** as a colorless oil (0.047 g, 73% yield).



[01317] **4-(4-(Chloromethyl)-2-((1R)-2,2-dimethyl-1-(methoxy)propyl)phenyl)-5-fluoro-2-(methoxy)pyridine or 4-(4-(chloromethyl)-2-((1S)-2,2-dimethyl-1-(methoxy)propyl)phenyl)-5-fluoro-2-(methoxy)pyridine (83.21L or 83.21M).** To a stirred solution of **83.21J or 83.21K** (0.047 g, 0.10 mmol) in DCM (1.0 mL) and DMF (0.0081 mL) at 0°C was added thionyl chloride (0.015 mL, 0.21 mmol). The reaction was then stirred at room temperature for one hour and concentrated in vacuo. The product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **83.21L or 83.21M** as a colorless solid (0.032 g, 87% yield).



83.21L or 83.21M

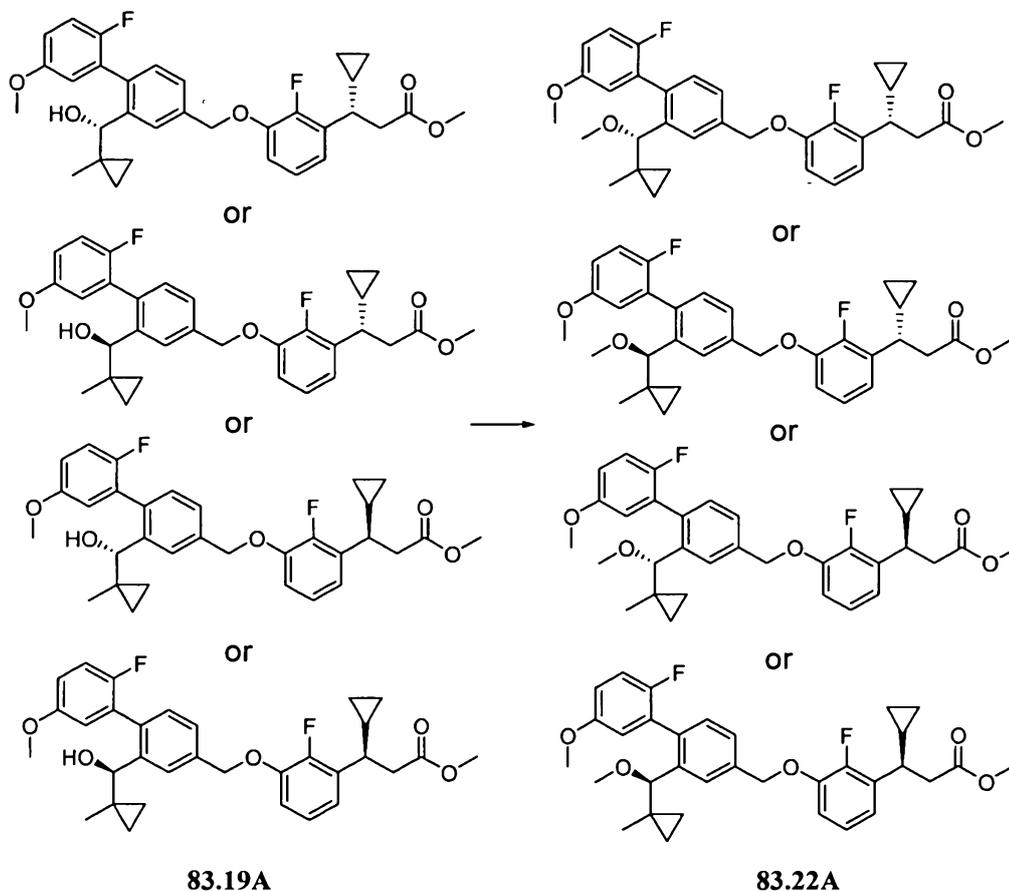
83

83.21N, 83.21O, 83.21P, or 83.21Q

[01318] (3S)-3-Cyclopropyl-3-(3-(((3-((1R)-2,2-dimethyl-1-(methoxy)propyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((3-((1S)-2,2-dimethyl-1-(methoxy)propyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((3-((1R)-2,2-dimethyl-1-(methoxy)propyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((3-((1S)-2,2-dimethyl-1-(methoxy)propyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)propanoic acid (83.21N, 83.21O, 83.21P, or 83.21Q). The alkylation and subsequent hydrolysis were conducted in an analogous manner to Example 66.6 (using the compound obtained from peak two of the chiral separation of 83.21E from the OD-

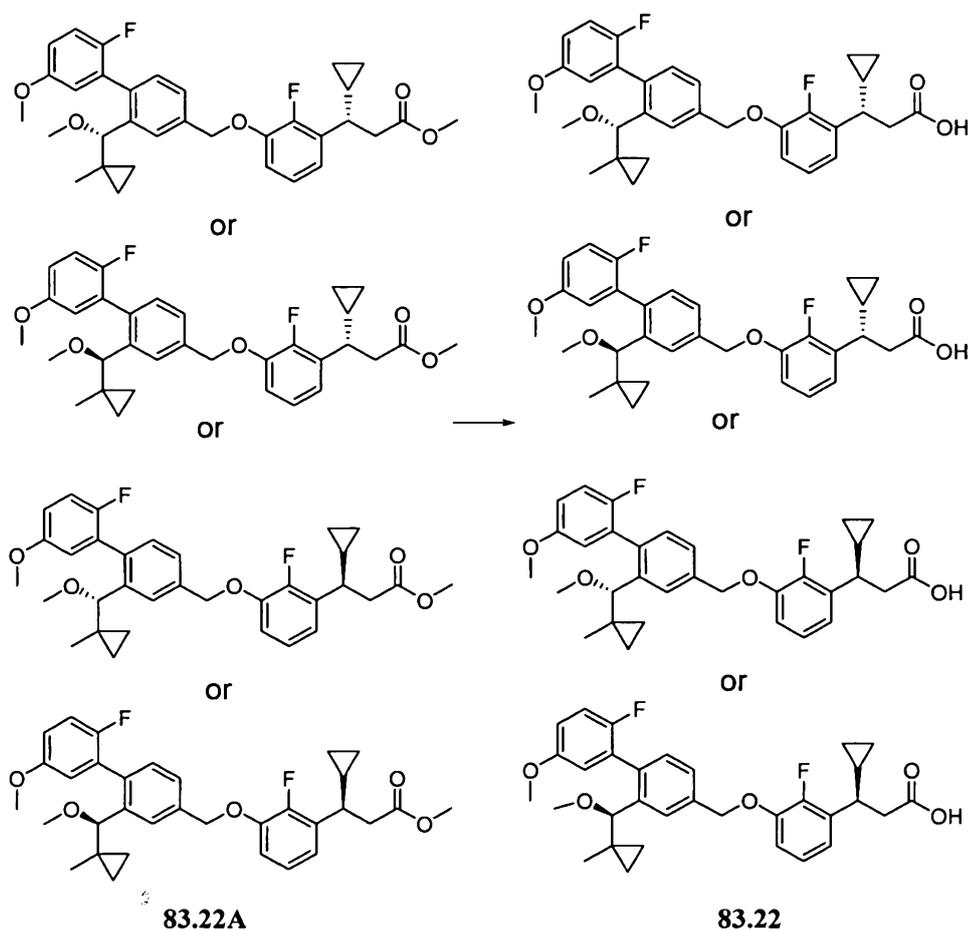
column, described herein) to yield **83.21N** or **83.21O** (0.0207 g, 40% yield over the two steps). MS ESI (neg.) m/e: 538.3 (M-H)⁺.

[01319] Example 83.22



[01320] Methyl (3S)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((S)-1-methylcyclopropyl)(methoxy)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3S)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((R)-1-methylcyclopropyl)(methoxy)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((S)-1-methylcyclopropyl)(methoxy)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate or methyl (3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((R)-1-methylcyclopropyl)(methoxy)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoate (83.22A**). A screw-cap vial was charged with **83.19A** (0.039 g, 0.073 mmol), DMF (0.4 mL), iodomethane (available from Aldrich)**

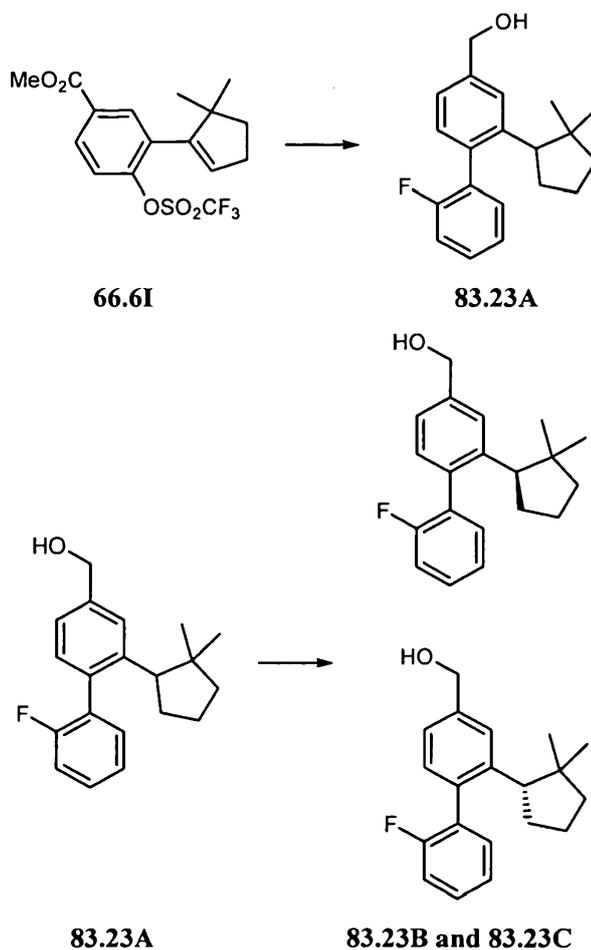
(0.0091 mL, 0.15 mmol), and sodium hydride (60% dispersion in mineral oil) (0.0052 g, 0.13 mmol). The mixture was stirred for 1 hour at room temperature, quenched with saturated aqueous NH_4Cl , and extracted with EtOAc. The combined organic layers were dried (MgSO_4) and concentrated. The crude product was purified by silica gel flash chromatography (0-15% EtOAc/hexane) to afford **83.22A** (0.0361 g, 90% yield) as a colorless oil.



[01321] (3S)-3-Cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((S)-(1-methylcyclopropyl)(methoxy)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((R)-(1-methylcyclopropyl)(methoxy)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((S)-(1-methylcyclopropyl)(methoxy)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((R)-(1-methylcyclopropyl)(methoxy)methyl)-5'-(methoxy)-1,1'-

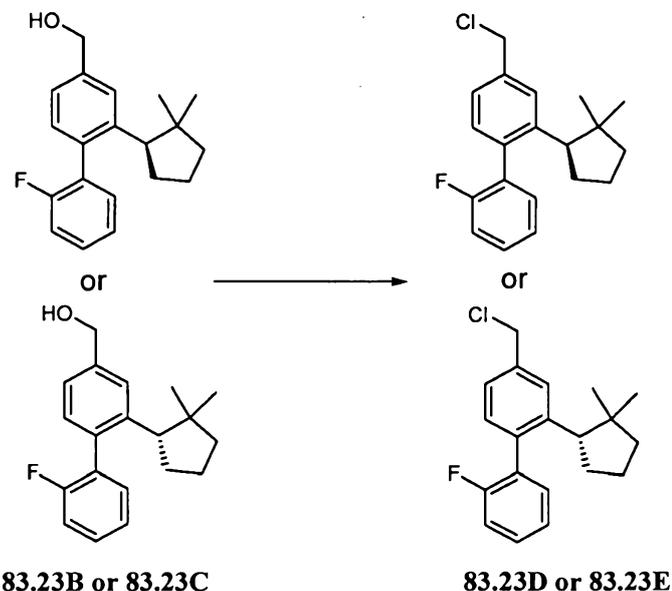
biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (83.22). Example 83.22 was prepared from 83.22A according to the analogous method described in Example 83.18. MS ESI (neg.) m/e: 535.2 (M-H)⁺.

[01322] **Example 83.23**



[01323] **(2-((1R)-2,2-Dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methanol and (2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methanol (83.2B and 83.23C).** A Suzuki hydrogenation and reduction strategy was employed similar to that of Example 66.6 using 2-fluorophenylboronic acid (commercially available from Aldrich) to yield alcohol 83.23A. Chiral separation of 83.23A was accomplished on Chiracel-OD (4%IPA in hexane) to provide 83.23B (peak one) and 83.23C (peak two). Both enantiomers were used to synthesize example

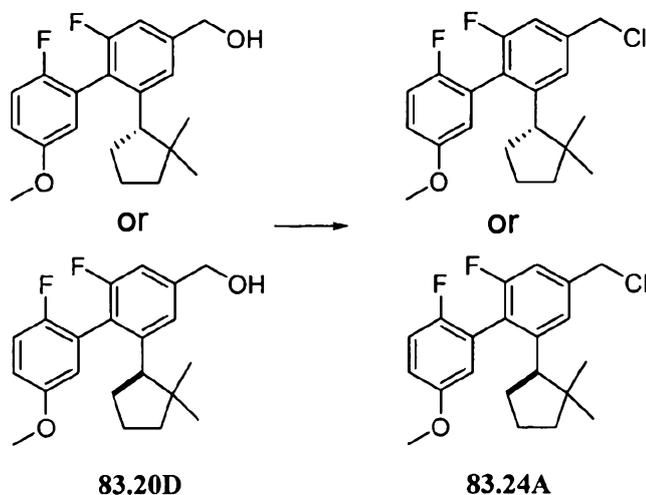
compounds, and both enantiomers gave active example compounds. However, the enantiomer corresponding to peak 2 provided the most active example compounds.



[01324] **4-(Chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl (83.23D or 83.23E).** To a stirred solution of **83.23B or 83.23C** (0.150 g, 0.50 mmol) in DCM (2.5 mL) and DMF (0.0039 mL) at 0°C was added thionyl chloride (0.073 mL, 1.0 mmol). The reaction was then stirred at room temperature for 1.5 hours. Next, the reaction mixture was concentrated in vacuo. The product was purified on silica gel (0-10% EtOAc in hexanes) to yield **83.23D or 83.23E** as a colorless oil (0.140 g, 88% yield).

[01325] **(3S)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid (83.23).** The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using **83.B** and **83.23D or 83.23E** derived from peak two from the chiral separation of **83.23A** from the OD-column, described herein) to yield **83.23** (0.0373 g, 71% yield over the two steps). MS ESI (neg.) m/e: 503.3 (M-H)⁺.

[01326]

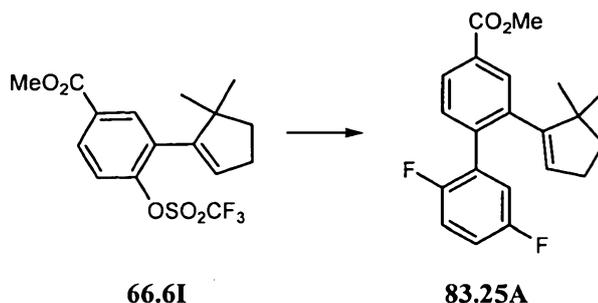
Example 83.24

[01327] **4-(Chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl (83.24A).** To a solution of **83.20D** (0.1492 g, 0.431 mmol) in dry DCM (4.5 mL) and dry DMF (0.035 mL) was added thionyl chloride (0.063 mL, 0.864 mmol) at 0 °C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 20 hours, the reaction was concentrated and then purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **83.24A** which was used without further purification (117.1 mg, 74% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.18 (1 H, d, J=1.6 Hz), 7.13 (2 H, m), 6.95 (1 H, m), 6.81 (1 H, m), 4.68 (2 H, m), 3.85 (3 H, m), 2.73 (1 H, ddd, J=10.3, 8.3, 1.8 Hz), 2.18 (1 H, m), 2.01 (1 H, m), 1.80 (1 H, d, J=4.3 Hz), 1.72 (3 H, m), 1.46 (1 H, m), 0.78 (3 H, s), 0.64 (3 H, s).

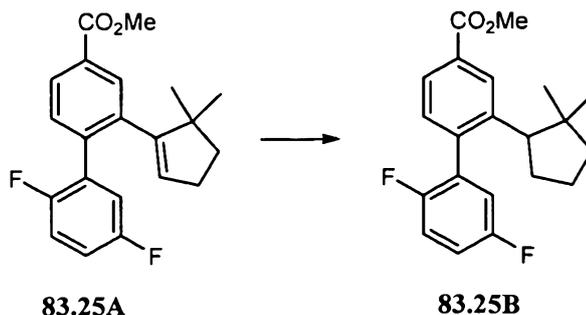
[01328] **(3S)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',6-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid (83.24).** The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using **83.B** and **83.24A** derived from peak two from the chiral separation of **83.20B** on the OJ-column,

described herein) to yield **83.24**. $^1\text{H NMR}$ (500 MHz, CDCl_3) δ ppm 7.23 (1 H, s), 7.12 (1 H, dd, $J=9.7, 1.6$ Hz), 7.07 (1 H, t, $J=8.8$ Hz), 7.03 (1 H, m), 6.93 (3 H, m), 6.78 (1 H, dd, $J=5.5, 3.1$ Hz), 5.19 (2 H, m), 3.79 (3 H, s), 2.86 (2 H, d, $J=7.3$ Hz), 2.76 (2 H, m), 2.19 (1 H, m), 2.04 (1 H, m), 1.86 (1 H, m), 1.71 (1 H, m), 1.57 (1 H, m), 1.43 (1 H, m), 1.20 (1 H, m), 0.73 (3 H, s), 0.65 (4 H, m), 0.46 (1 H, m), 0.34 (1 H, dq, $J=9.8, 4.8$ Hz), 0.20 (1 H, dq, $J=9.6, 4.9$ Hz). MS ESI (neg.) m/e : 551.1 (M-H) $^+$.

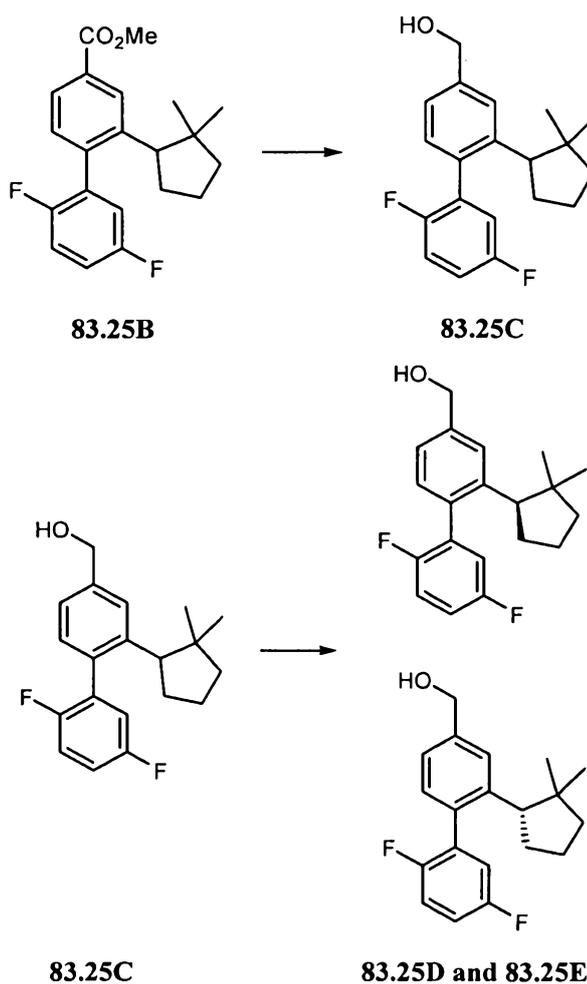
[01329] **Example 83.25**



[01330] **Methyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-2',5'-difluoro-1,1'-biphenyl-4-carboxylate (83.25A)**. To a stirred solution of methyl 3-(5,5-dimethylcyclopent-1-en-1-yl)-4-(trifluoromethylsulfonyloxy)benzoate **66.6I** (0.50 g, 1 mmol) in DMF (7 mL) at 23°C was added 2,5-difluorophenylboronic acid (0.3 g, 2 mmol, commercially available from Aldrich), and potassium carbonate (0.5 g, 4 mmol). Tetrakis(triphenylphosphine)palladium (0.2 g, 0.1 mmol) was then added to the mixture. The mixture was heated to 90°C and the reaction was further stirred for 23 hours. The reaction was then cooled to room temperature, diluted with brine and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was purified on silica gel (0-10% EtOAc in hexanes) to yield **83.25A** as a colorless oil (0.42 g, 93% yield).



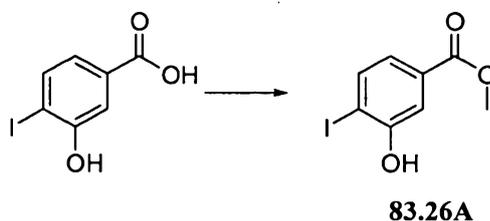
[01331] **Methyl 2-(2,2-dimethylcyclopentyl)-2',5'-difluoro-1,1'-biphenyl-4-carboxylate (83.25B)**. To a stirred solution of **83.25A** (0.420 g, 1 mmol) in MeOH (5 mL) at 23°C was added palladium on carbon (0.1 g). The reaction was placed under an atmosphere of hydrogen and stirred for 18 hours. The reaction mixture was then filtered and concentrated in vacuo. The product was purified on silica gel (0-10% EtOAc in hexanes) to yield **83.25B** as a colorless oil (0.420 g, 99% yield)



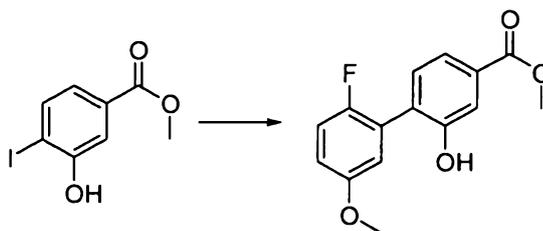
[01332] **(2-((1R)-2,2-Dimethylcyclopentyl)-2',5'-difluoro-1,1'-biphenyl-4-yl)methanol and (2-((1S)-2,2-dimethylcyclopentyl)-2',5'-difluoro-1,1'-biphenyl-4-yl)methanol (83.25D and 83.25E)**. To a stirred solution of **83.25B** (0.420 g, 1.2 mmol) in THF (10.00 mL) at 0°C was added LAH (2.4 mL, 2.4 mmol, 1.0M). The reaction was stirred for one hour and then 1N NaOH(aq) was added to quench the reaction. The reaction was extracted three times with EtOAc. After drying over anhydrous magnesium

[01334] (3S)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5'-difluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5'-difluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5'-difluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5'-difluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid (83.25). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 83.B and 83.25F or 83.25G derived from peak two from the chiral separation of 83.25C from the OD-column, described herein) to yield 83.25 (0.0464 g, 84% yield over the two steps). MS ESI (neg.) m/e: 521.2 (M-H)⁺.

[01335] **Example 83.26**

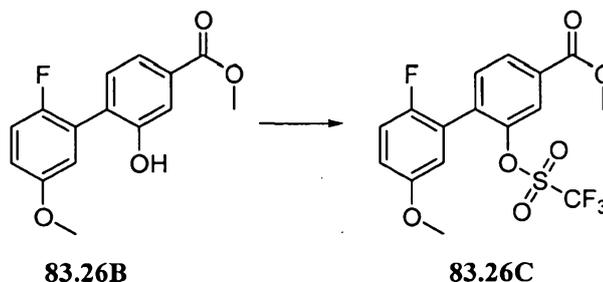


[01336] **Methyl 3-hydroxy-4-iodobenzoate (83.26A)**. To a round bottom flask containing 3-hydroxy-4-iodobenzoic acid (1.0346 g, 3.92 mmol, commercially available from Aldrich) was added a cold solution of MeOH (15 mL) and sulfuric acid (0.5 mL). The mixture was heated to 80°C and monitored with TLC. After 20.5 hours, the solvent was removed and the residue was diluted with EtOAc. The organic phase was washed carefully two times with saturated aqueous NaHCO₃, once with brine, and then dried over anhydrous sodium sulfate. After filtration, the organic solvent was removed in vacuo to afford 83.26A as a white solid (1.0938 g, 100% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.76 (1 H, d, J=8.2 Hz), 7.64 (1 H, d, J=2.0 Hz), 7.34 (1 H, dd, J=8.2, 2.0 Hz), 3.92 (3 H, s).



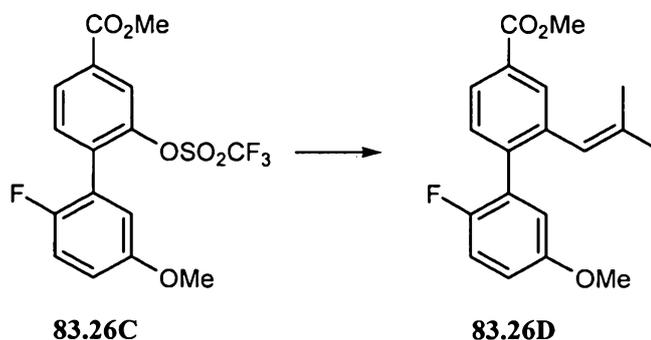
83.26A**83.26B**

[01337] **Methyl 2'-fluoro-2-hydroxy-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (83.26B)**. To a round bottom flask containing **83.26A** (1.0938 g, 3.93 mmol) and 2-fluoro-5-methoxyphenylboronic acid (0.7053 g, 4.15 mmol)(commercially available from Aldrich) was added a premixed solution of 1:1 isopropanol (6 mL) and water (6 mL). After stirring at room temperature for 5 minutes, sodium carbonate (0.5526 g, 5.21 mmol) and palladium, 10 wt% on activated carbon (0.0725 g, 0.0681 mmol) were added, and the reaction was then heated to 65°C. After 17 hours, the reaction was cooled to room temperature and then filtered through Celite. The filtrate was concentrated and then saturated aqueous ammonium chloride was added. After extracting three times with EtOAc, the organic solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (0-40% EtOAc/hexane) to afford **83.26B** (834.3 mg, 77% yield). ¹H NMR (500 MHz, CDCl₃) δ ppm 7.69 (2 H, td, J=7.7, 1.7 Hz), 7.33 (1 H, d, J=7.8 Hz), 7.14 (1 H, t, J=9.0 Hz), 6.94 (1 H, dt, J=9.0, 3.5 Hz), 6.89 (1 H, dd, J=5.9, 3.2 Hz), 5.42 (1 H, s), 3.94 (3 H, s), 3.82 (3 H, s).

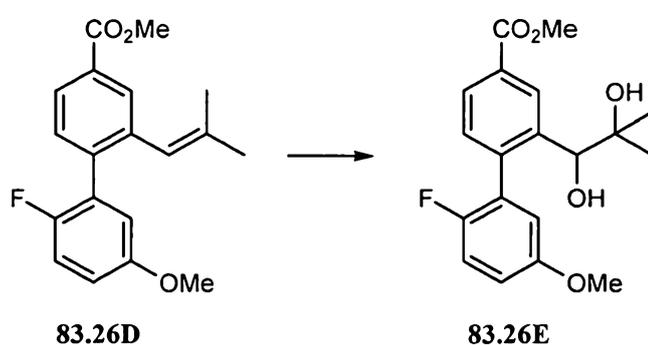
**83.26B****83.26C**

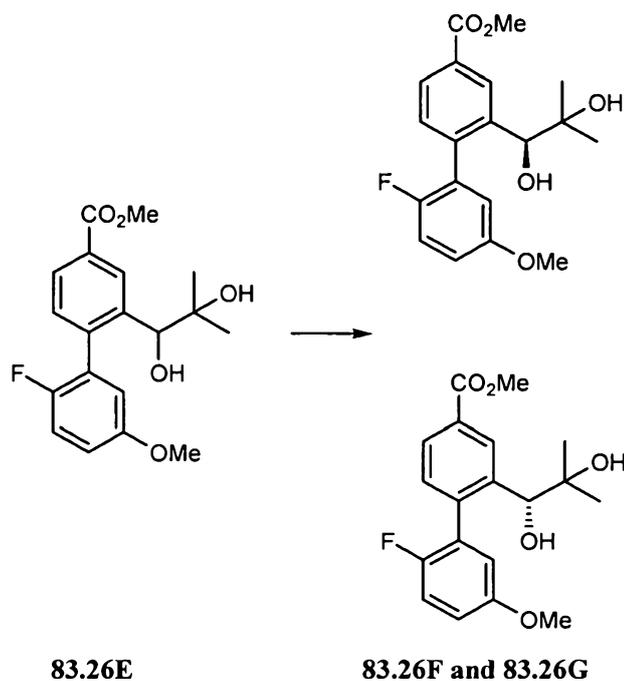
[01338] **Methyl 2'-fluoro-5'-(methoxy)-2-(((trifluoromethyl)sulfonyl)oxy)-1,1'-biphenyl-4-carboxylate (83.26C)**. To a stirred solution of **83.26B** (0.8343 g, 3 mmol) in dry DCM (12 mL) was added TEA (0.85 mL, 6 mmol) and 4-dimethylaminopyridine (0.0378 g, 0.3 mmol). After 20 minutes, N-phenyl-bis(trifluoromethanesulfonimide) (1.3097 g, 4 mmol) was added in portions. Upon complete addition, the solution was stirred at room temperature. After 3 hours, the reaction was diluted with brine and extracted three times with DCM. After drying over anhydrous magnesium sulfate and filtration, the organic solvent was removed under reduced pressure and the residue was then purified by silica gel flash chromatography (0-25% EtOAc/hexane) to afford **83.26C** (1.0238 g, 83% yield). ¹H NMR (500 MHz, CDCl₃) δ ppm 8.14 (1 H, dd, J=8.1, 1.7 Hz), 8.06 (1 H, d, J=1.7 Hz), 7.57 (1 H, d, J=8.1

Hz), 7.13 (1 H, t, J=9.2 Hz), 6.97 (1 H, ddd, J=8.7, 3.9, 3.5 Hz), 6.87 (1 H, dd, J=5.7, 3.1 Hz), 3.99 (3 H, s), 3.83 (3 H, s).

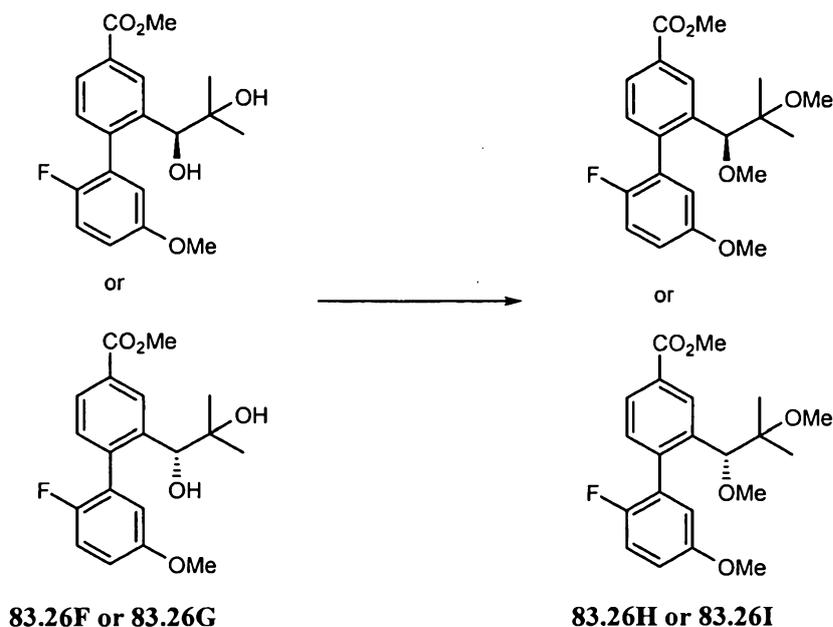


[01339] Methyl 2'-fluoro-5'-(methoxy)-2-(2-methyl-1-propenyl)-1,1'-biphenyl-4-carboxylate (83.26D). To a stirred solution of **83.26C** (0.500 g, 1.2 mmol) in DMF (6.1 mL) at 23°C was added 2-methylprop-1-enylboronic acid (0.24 g, 2.4 mmol, commercially available from Synthonix), and potassium carbonate (0.51 g, 3.7 mmol). Tetrakis(triphenylphosphine)palladium (0.071 g, 0.061 mmol) was then added to the mixture. The mixture was heated to 90°C and stirred for 15 hours. The reaction was then cooled to room temperature, diluted with brine and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **83.26D** as a colorless oil (0.280 g, 73% yield).

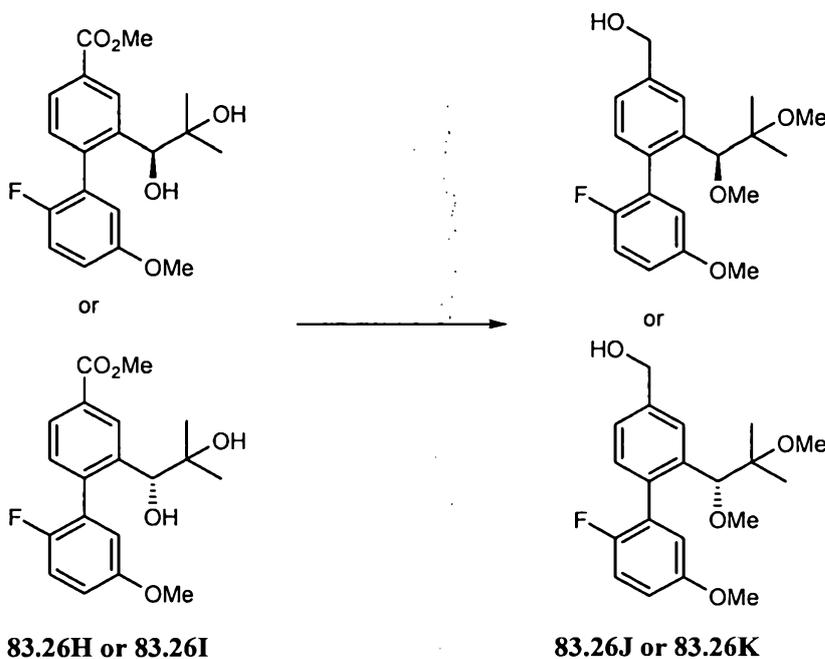




[01340] Methyl 2-((1S)-1,2-dihydroxy-2-methylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate and Methyl 2-((1R)-1,2-dihydroxy-2-methylpropyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (**83.26F** and **83.26G**). To a stirred solution of **83.26D** (0.270 g, 0.86 mmol) in propan-2-one (10.00 mL) at 23°C was added 4-methylmorpholine n-oxide monohydrate (0.12 g, 0.86 mmol), followed by osmium tetroxide (0.027 mL, 0.086 mmol). The reaction was then stirred for six hours and then concentrated in vacuo. The product was purified on silica gel (0-10% EtOAc in hexanes) to yield **83.26E** as a colorless oil (0.250 g, 84% yield). Chiral separation of **83.26E** was accomplished on Chiracel-OD (5%IPA in hexane) to provide **83.26F** (peak one) and **83.26G** (peak two). Both enantiomers were used to synthesize example compounds, and both enantiomers gave active example compounds. However, the enantiomer corresponding to peak one provided the most active example compounds.



[01341] **Methyl 2'-fluoro-2-((1S)-2-methyl-1,2-bis(methoxy)propyl)-5'-(methoxy)-1,1'-biphenyl-4-carboxylate or methyl 2'-fluoro-2-((1R)-2-methyl-1,2-bis(methoxy)propyl)-5'-(methoxy)-1,1'-biphenyl-4-carboxylate (83.26H and 83.26I).** To a stirred solution of **83.26F** or **83.26G** (peak one from the chiral separation of **83.26E**) (0.104 g, 0.30 mmol) in DMF (3.0 mL) at 23°C was added iodomethane (0.074 mL, 1.2 mmol), followed by sodium hydride (0.029 g, 1.2 mmol). The reaction was then stirred at 50°C for 16 hours and then cooled to room temperature. The reaction was diluted with brine and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **83.26H** or **83.26I** as a colorless oil (0.079 g, 70% yield).

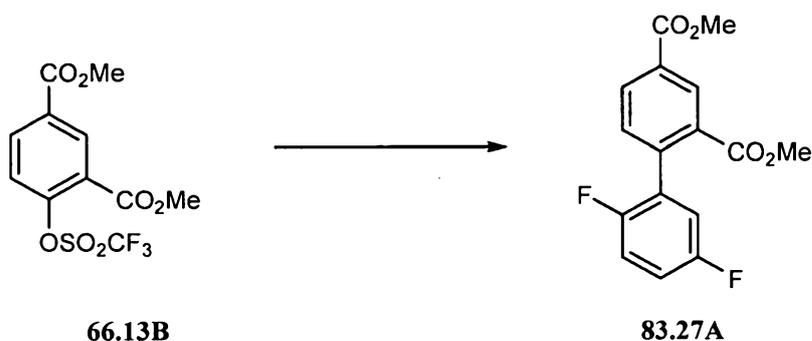


[01342] **(2'-Fluoro-2-((1S)-2-methyl-1,2-bis(methoxy)propyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol** or **(2'-fluoro-2-((1R)-2-methyl-1,2-bis(methoxy)propyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methanol** (**83.26J** or **83.26K**). To a stirred solution of **83.26H** or **83.26I** (0.079 g, 0.21 mmol) in THF (3.00 mL, 0.21 mmol) at 0°C was added LAH (0.42 mL, 0.42 mmol). The reaction was then stirred for two hours. Next, 1N NaOH(aq) was added to quench the reaction. The reaction was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **83.26J** or **83.26K** as a colorless oil (0.058 g, 79% yield).

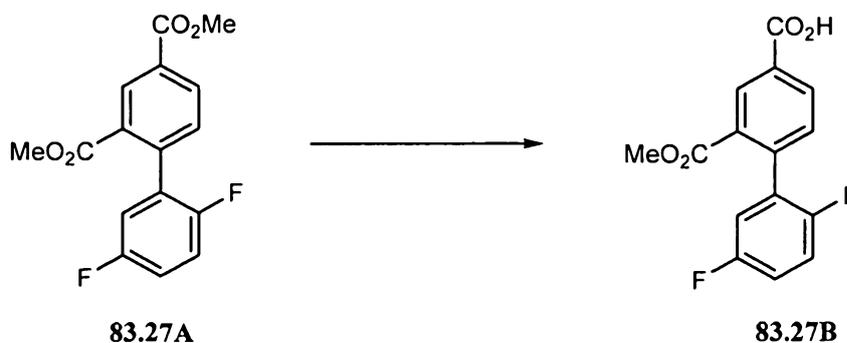
[01343] **(3S)-3-Cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1S)-2-methyl-1,2-bis(methoxy)propyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid** or **(3S)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1R)-2-methyl-1,2-bis(methoxy)propyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid** or **(3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1S)-2-methyl-1,2-bis(methoxy)propyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid** or **(3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1R)-2-methyl-1,2-bis(methoxy)propyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid** (**83.26**). The Mitsunobu reaction and hydrolysis

were conducted in an analogous manner to Example 69.14 (using **83B** and **83.26J** or **83.26K** derived from peak one from the chiral separation of **83.26E** from the OD-column, described herein) to yield **83.26** (0.0681 g, 68% yield). MS ESI (neg.) m/e: 553.3 (M-H)⁺.

[01344] **Example 83.27**

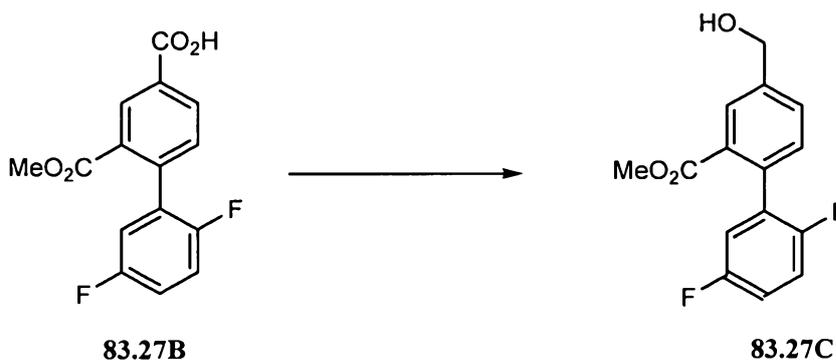


[01345] **Dimethyl 2',5'-difluoro-1,1'-biphenyl-2,4-dicarboxylate (83.27A).** To a stirred solution of dimethyl 4-(trifluoromethylsulfonyloxy)isophthalate **66.13B** (1.00 g, 2.9 mmol) in DMF (5.8 mL) at 23°C was added 2,5-difluorophenylboronic acid (0.69 g, 4.4 mmol)(commercially available from Aldrich), and potassium carbonate (1.2 g, 8.8 mmol). Tetrakis(triphenylphosphine)palladium (0.24 g, 0.20 mmol) was then added to the mixture. The mixture was heated to 90°C and was stirred for 17 hours. The reaction was then cooled to room temperature, diluted with brine and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **83.27A** as a colorless oil (0.800 g, 89% yield).

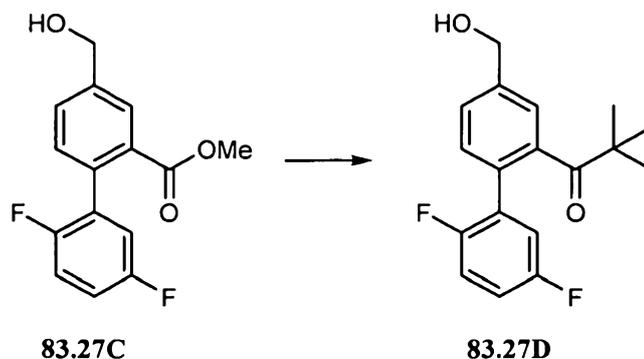


[01346] **2',5'-Difluoro-2-((methoxy)carbonyl)-1,1'-biphenyl-4-carboxylic acid (83.27B).** To a stirred solution of **83.27A** (0.800 g, 2.6 mmol) in THF (7.00 mL)

and MeOH (7.00 mL) at 0°C was slowly added potassium hydroxide (1.4 mL, 2.9 mmol) to maintain the temperature below 6°C. The reaction mixture was then allowed to warm to room temperature and stirred for 19 hours. The reaction was then acidified with 1N HCl and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure to yield **83.27B** as a colorless solid (0.76 g, 100% yield).

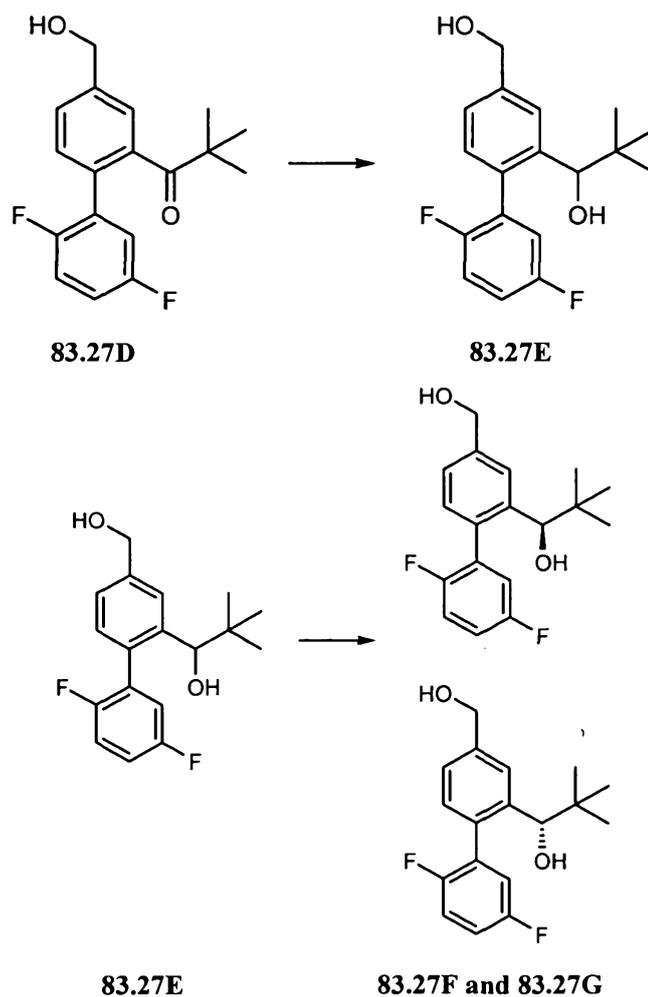


[01347] **Methyl 2',5'-difluoro-4-(hydroxymethyl)-1,1'-biphenyl-2-carboxylate (83.27C)**. To a stirred solution of **83.27B** (0.585 g, 2 mmol) in THF (20 mL) at 0°C was added borane-THF (4 mL, 4 mmol, 1.0M). The reaction was warmed to 23°C and stirring was continued for four hours. The reaction mixture was then concentrated in vacuo. The reaction was diluted with 1N HCl and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-40% EtOAc in hexanes) to yield **83.27C** as a colorless oil (0.485 g, 87% yield).



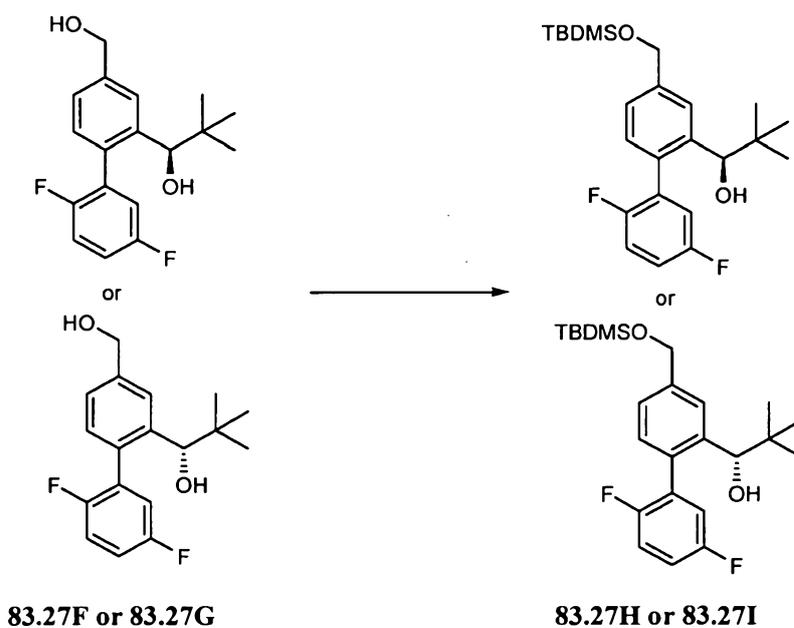
[01348] **1-(2',5'-Difluoro-4-(hydroxymethyl)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanone (83.27D)**. To a stirred solution of **83.27C** (0.485 g, 2 mmol) in THF (17

mL) at -78°C was added tert butyl lithium (3 mL, 5 mmol, 1.7 M). The reaction was then stirred for 1.5 hours and then quenched with a saturated solution of ammonium chloride and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-40% EtOAc in hexanes) to yield **83.27D** as a colorless oil (0.450 g, 85% yield).

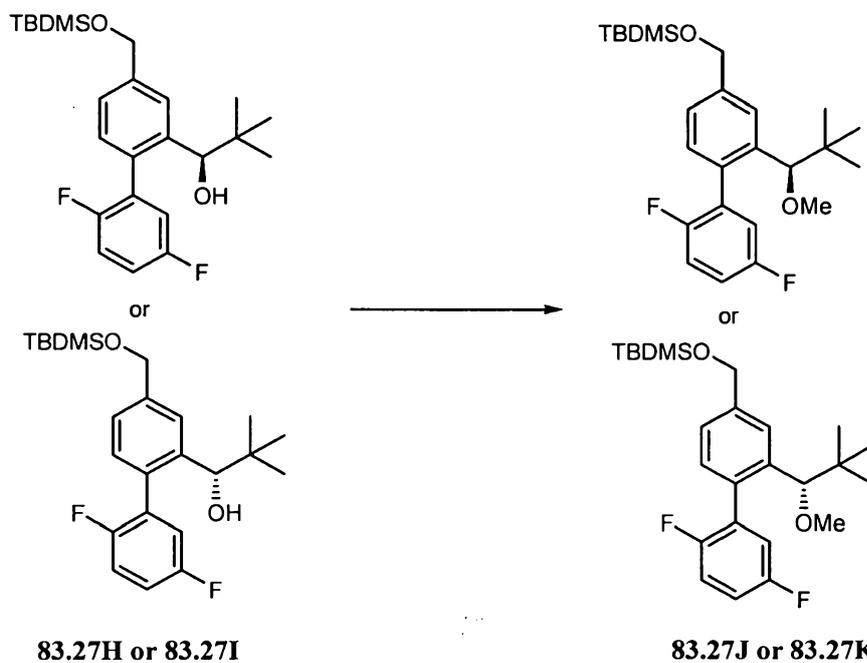


[01349] (1R)-1-(2',5'-Difluoro-4-(hydroxymethyl)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol and (1S)-1-(2',5'-difluoro-4-(hydroxymethyl)-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol (**83.27F** and **83.27G**). To a stirred solution of **83.27D** (0.286 g, 0.9 mmol) in THF (5 mL) at 0°C was added LAH (1 mL, 1 mmol, 1.0 M). The reaction was then stirred for 3 hours. 1N NaOH(aq) was added to quench the reaction,

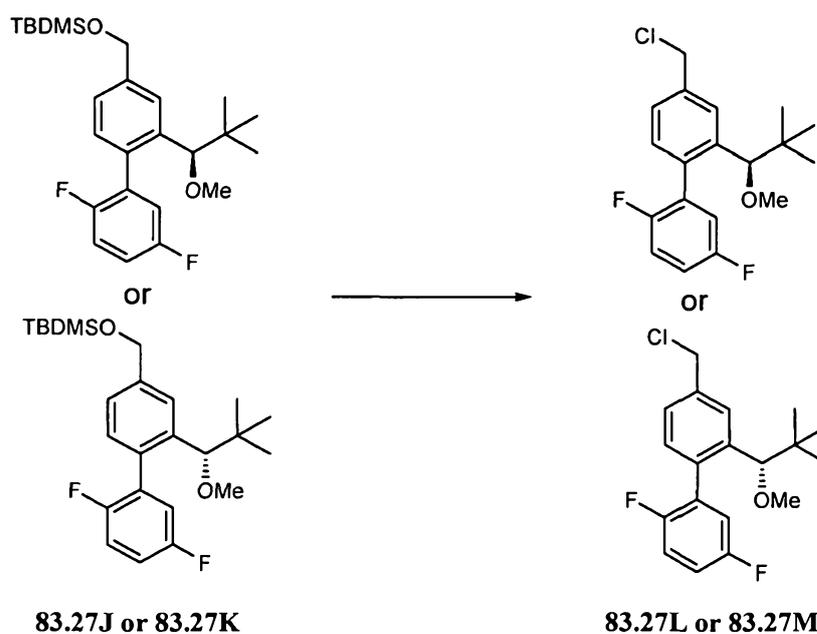
and the mixture was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **83.27E** as a colorless oil (0.250 g, 87% yield). Chiral separation of **83.27E** was accomplished on Chiracel-OD (4%IPA in hexane) to provide **83.27F** (peak one-20.4 mins) and **83.27G** (peak two-26.1 mins). Both enantiomers were used to synthesize example compounds, and both enantiomers gave active example compounds. However, the enantiomer corresponding to peak 2 provided the most active example compounds.¹



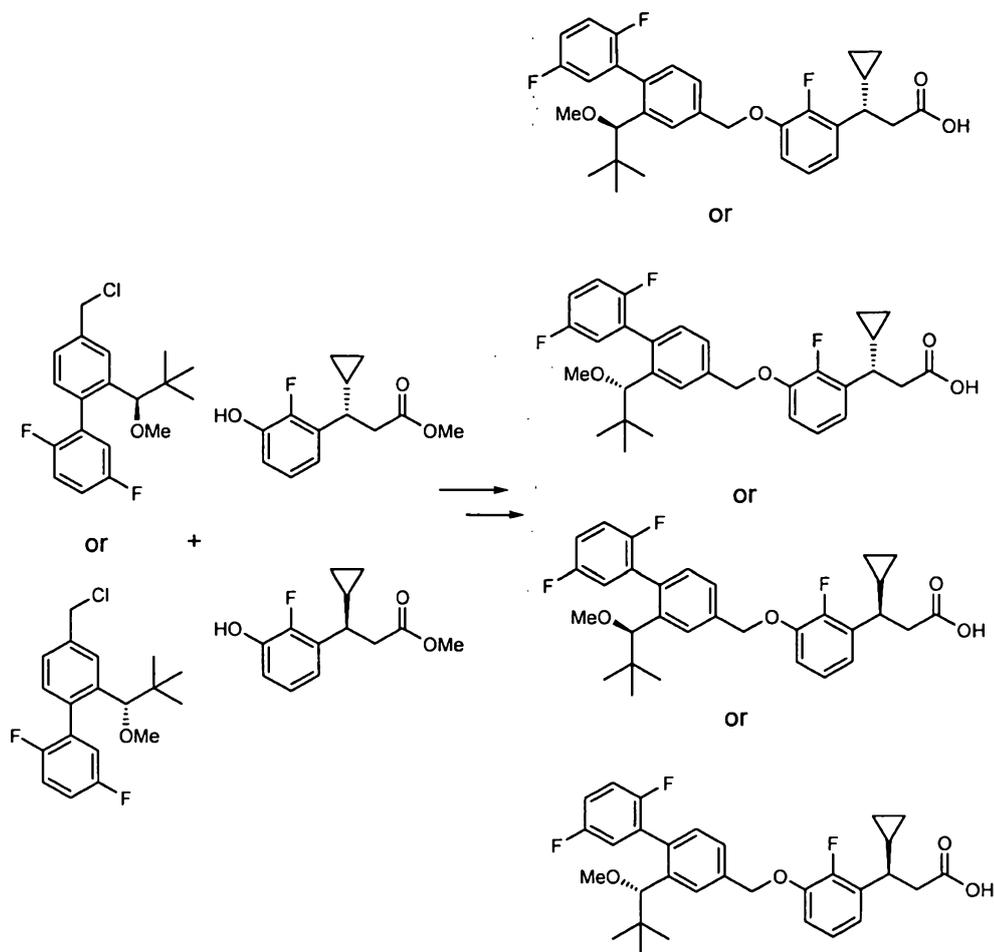
[01350] (1R)-1-(4-(((1,1-Dimethylethyl)(dimethyl)silyl)oxy)methyl)-2',5'-difluoro-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol or (1S)-1-(4-(((1,1-dimethylethyl)(dimethyl)silyl)oxy)methyl)-2',5'-difluoro-1,1'-biphenyl-2-yl)-2,2-dimethyl-1-propanol (**83.27H or 83.27I**). To a stirred solution of **83.27F or 83.27G** (0.097 g, 0.3 mmol) in DCM (3 mL) at 23°C was added tert-butyldimethylsilyl chloride (0.06 mL, 0.4 mmol), followed by TEA (0.05 mL, 0.4 mmol) and DMAP (0.004 g, 0.03 mmol). The reaction was then stirred for 24 hours and then concentrated in vacuo. The reaction was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **83.27H or 83.27G** as a colorless oil (0.130 g, 98% yield).



[01351] (1,1-Dimethylethyl)((2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2',5'-difluoro-1,1'-biphenyl-4-yl)methyl)oxy)dimethylsilane or (1,1-dimethylethyl)((2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2',5'-difluoro-1,1'-biphenyl-4-yl)methyl)oxy)dimethylsilane (83.27J or 83.27K). To a stirred solution of 83.27H or 83.27I (0.130 g, 0.31 mmol) in DMF (3.1 mL) at 23°C was added iodomethane (0.038 mL, 0.62 mmol), followed by sodium hydride (0.015 g, 0.62 mmol). The reaction was then stirred at 50°C for 16 hours, diluted with water and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-5% EtOAc in hexanes) to yield 83.27J or 83.27K as a colorless oil (0.125 g, 93% yield).



[01352] **4-(Chloromethyl)-2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2',5'-difluoro-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2',5'-difluoro-1,1'-biphenyl (83.27L or 83.27M).** To a stirred solution of **83.27J or 83.27K** (0.125 g, 0.29 mmol) in DCM (2.9 mL) and DMF (0.022 mL) at 0°C was added thionyl chloride (0.042 mL, 0.58 mmol). The reaction was then stirred at room temperature for three hours. The reaction mixture was then concentrated in vacuo, and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **83.27L or 83.27M** as a colorless oil (0.097 g, 100% yield).

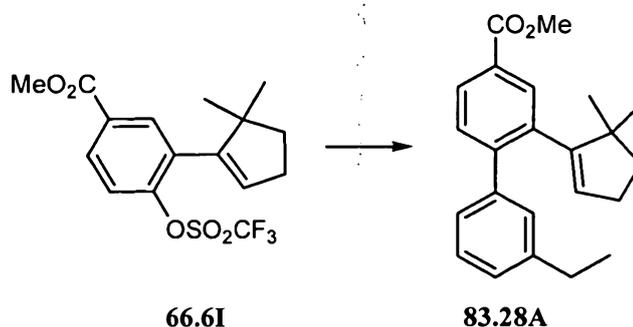


83.27L or 83.27M

83.B

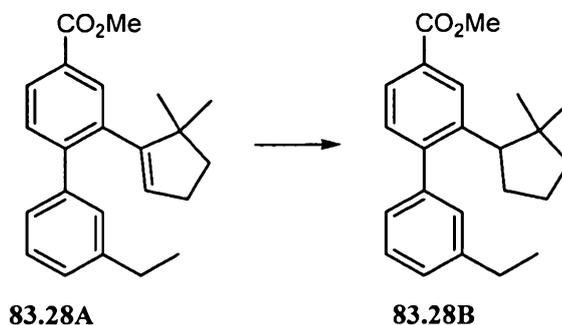
83.27

[01353] (3S)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2',5'-difluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2',5'-difluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethyl-1-(methoxy)propyl)-2',5'-difluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethyl-1-(methoxy)propyl)-2',5'-difluoro-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid (83.27). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 83.B and 83.27L or 83.27M derived from peak two from the chiral separation of 83.27E from the OD-column, described herein) to yield 83.27N or 83.27O (0.0377 g, 68% yield). MS ESI (neg.) m/e: 525.3 (M-H)⁺.

[01354] **Example 83.28**

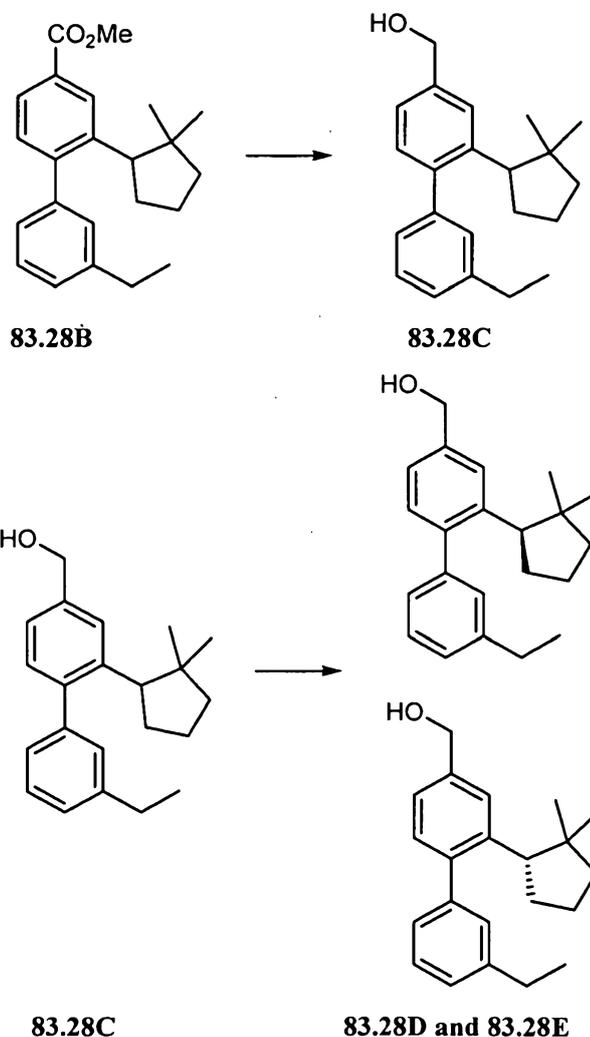
[01355] **Methyl 2-(5,5-dimethyl-1-cyclopenten-1-yl)-3'-ethyl-1,1'-biphenyl-4-carboxylate (83.28A).** To a stirred solution of methyl 3-(5,5-dimethylcyclopent-1-enyl)-4-(trifluoromethylsulfonyloxy)benzoate **66.6I** (0.50 g, 1 mmol) in DMF (7 mL) at 23°C was added 3-ethylphenylboronic acid (0.3 g, 2 mmol)(commercially available from Aldrich), and potassium carbonate (0.5 g, 4 mmol).

Tetrakis(triphenylphosphine)palladium (0.2 g, 0.1 mmol) was then added to the mixture. The mixture was heated to 90°C and the reaction was stirred for 24 hours. The reaction was then cooled to room temperature, diluted with brine and extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-10% EtOAc in hexanes) to yield **83.28A** as a colorless oil (0.41 g, 93% yield).



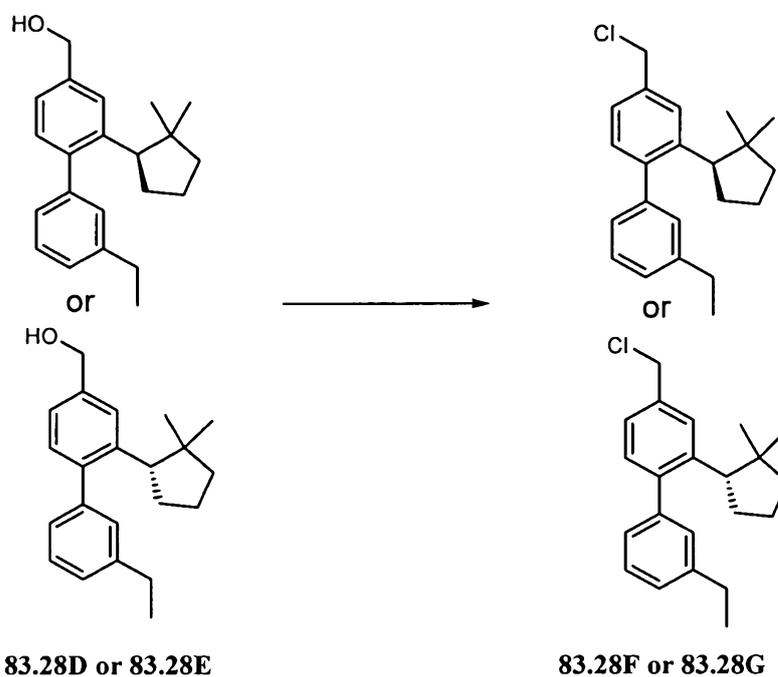
[01356] **Methyl 2-(2,2-dimethylcyclopentyl)-3'-ethyl-1,1'-biphenyl-4-carboxylate (83.28B).** To a stirred solution of **83.28A** (0.410 g, 1 mmol) in MeOH (5 mL) at 23°C was added palladium on carbon (0.1 g, 1 mmol). The reaction was placed under an atmosphere of hydrogen and stirred for 18 hours. The reaction mixture was then

filtered and the filtrate was concentrated in vacuo. The product was purified on silica gel (0-10% EtOAc in hexanes) to yield **83.28B** as a colorless oil (0.410 g, 99% yield).



[01357] (2-((1R)-2,2-Dimethylcyclopentyl)-3'-ethyl-1,1'-biphenyl-4-yl)methanol and (2-((1S)-2,2-dimethylcyclopentyl)-3'-ethyl-1,1'-biphenyl-4-yl)methanol (**83.28D** and **83.28E**). To a stirred solution of **83.28B** (0.410 g, 1.2 mmol) in THF (10.00 mL) at 0°C was added LAH (2.4 mL, 2.4 mmol, 1.0M). The reaction was then stirred for 1.5 hours. 1 N NaOH(aq) was added to quench the reaction. The mixture was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate and filtering, the organic solvent was removed under reduced pressure and the product was then purified on silica gel (0-20% EtOAc in hexanes) to yield **83.28C** as a colorless oil (0.300 g, 80% yield). Chiral separation of **83.28C** was accomplished on Chiracel-OD

(4%IPA in hexane) to provide **83.28D** (peak one) and **83.28E** (peak two). Both enantiomers were used to synthesize example compounds, and both enantiomers gave active example compounds. However, the enantiomer corresponding to peak 2 provided the most active example compounds.



[01358] **4-(Chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-3'-ethyl-1,1'-biphenyl or 4-(chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-3'-ethyl-1,1'-biphenyl (83.28F or 83.28G).** To a stirred solution of **83.28D** or **83.28E** (0.130 g, 0.42 mmol) in DCM (2.1 mL) and DMF (0.0033 mL) at 0°C was added thionyl chloride (0.062 mL, 0.84 mmol). The reaction was then stirred at room temperature for 1.5 hours and then concentrated in vacuo. The resulting product was purified on silica gel (0-10% EtOAc in hexanes) to yield **83.28F** or **83.28G** as a colorless oil (0.120 g, 87% yield).

[01359] **(3S)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-3'-ethyl-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-3'-ethyl-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-3'-ethyl-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-3'-ethyl-1,1'-biphenyl-4-yl)methyl)oxy)-2-**

fluorophenyl)propanoic acid (83.28). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 83.B and 83.28F or 83.28G derived from peak two from the chiral separation of 83.28C from the OD-column, described herein) to yield 83.28 (0.0411 g, 76% yield over the two steps). MS ESI (neg.) m/e: 513.3 (M-H)⁺.

[01360] **(3S)-3-(3-(((2-(1-Azepanylmethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)-3-cyclopropylpropanoic acid or (3R)-3-(3-(((2-(1-Azepanylmethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)-3-cyclopropylpropanoic acid (83.29).** The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 83.B and 66.73C described herein) to yield 83.29. After removing solvent, 83.29 was obtained as TFA salt (51mg). MS ESI (neg.) m/e: 544 (M-H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 9.40 (m, 1H), 7.91 (m, 1H), 7.64-7.66 (m, 1H), 7.44 (m, 1H), 7.27-7.32 (m, 1H), 7.06-7.15 (m, 3H), 6.86-7.00 (m, 2H), 5.23 (s, 2H), 4.04-4.36 (m, 1H), 3.78 (s, 3H), 3.14 (m, 1H), 2.90 (m, 1H), 2.86 (m, 1H), 2.70 (m, 2H), 2.65 (m, 1H), 1.49 (m, 8H), 1.05 (m, 1H), 0.53 (m, 1H), 0.27-0.53 (m, 2H), 0.08 (m, 1H).

[01361] **(3S)-3-(3-(4-(5-Fluoro-2-methoxypyridin-4-yl)-3-(1-(methoxymethyl)cyclopentyl)benzyloxy)-2-fluorophenyl)-3-cyclopropylpropanoic acid or (3R)-3-(3-(4-(5-fluoro-2-methoxypyridin-4-yl)-3-(1-(methoxymethyl)cyclopentyl)benzyloxy)-2-fluorophenyl)-3-cyclopropylpropanoic acid (83.30).** The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 83.B and 77.12C, described herein) to yield 83.30. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.77 (1 H, s), 7.04 - 7.14 (1 H, m), 7.03 (1 H, s), 6.71 - 6.81 (2 H, m), 6.57 - 6.71 (2 H, m), 6.49 (1 H, d, J=4.7 Hz), 4.87 - 4.97 (2 H, m), 3.71 (3 H, s), 2.97 - 3.11 (2 H, m), 2.98 (3 H, s), 2.52 - 2.70 (3 H, m), 2.33 - 2.52 (1 H, m), 1.66 - 1.80 (1 H, m), 1.44 - 1.59 (2 H, m), 1.23 - 1.44 (4 H, m), 0.89 (1 H, dd, J=8.2, 3.5 Hz), 0.28 - 0.43 (1 H, m), 0.17 (1 H, td, J=8.7, 4.5 Hz), 0.09 (1 H, dd, J=9.2, 4.5 Hz), -0.08 - 0.04 (1 H, m). MS ESI (pos.) m/e: 552.2 (M+H)⁺.

[01362] **Example 83.31**

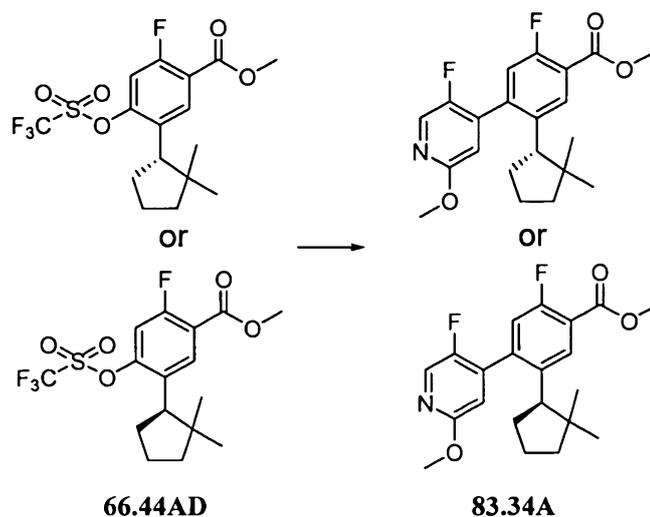
[01363] **(3S)-3-Cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((R)-(1-methylcyclopropyl)(methoxy)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((S)-(1-methylcyclopropyl)(methoxy)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(2-fluoro-**

3-(((2'-fluoro-2-((R)-(1-methylcyclopropyl)(methoxy)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((S)-(1-methylcyclopropyl)(methoxy)methyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (83.31). 83.31 was prepared from 83.18I according to the analogous methods described in Example 83.22. MS ESI (neg.) m/e: 535.2 (M-H)⁺.

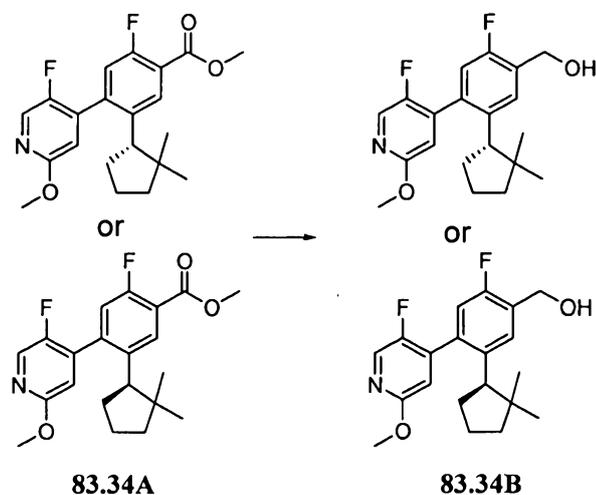
[01364] (3S)-3-Cyclopropyl-3-(3-(((3-((1R)-2,2-dimethyl-1-(methoxy)propyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((3-((1S)-2,2-dimethyl-1-(methoxy)propyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((3-((1R)-2,2-dimethyl-1-(methoxy)propyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((3-((1S)-2,2-dimethyl-1-(methoxy)propyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)propanoic acid (83.32). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 83.B and 83.21L or 83.21M derived from peak one from the chiral separation of 83.21E from the OD-column, described herein) to yield 83.32 (0.0252 g, 48% yield over the two steps). MS ESI (neg.) m/e: 538.2 (M-H)⁺.

[01365] (3S)-3-Cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1S)-2-methyl-1,2-bis(methoxy)propyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1R)-2-methyl-1,2-bis(methoxy)propyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1S)-2-methyl-1,2-bis(methoxy)propyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1R)-2-methyl-1,2-bis(methoxy)propyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (83.33). The Mitsunobu reaction and hydrolysis were conducted in an analogous manner to Example 69.14 (using 83.B and 83.26J or 83.26K peak two from the chiral separation of 83.26E from the OD-column, described herein) to yield 83.33A or 83.33B. (MS ESI (neg.) m/e: 553.2 (M-H)⁺.

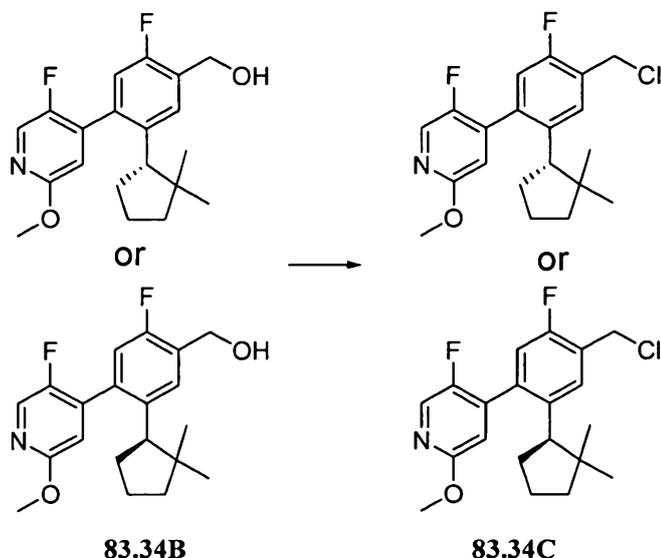
[01366] Example 83.34



[01367] **Methyl 5-((1S)-2,2-dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methoxy)-4-pyridinyl)benzoate or methyl 5-((1R)-2,2-dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methoxy)-4-pyridinyl)benzoate (83.34A).** To a stirred solution of **66.44AD** (0.7937 g, 1.992 mmol) in DMF (4 mL) at 23 °C was added 5-fluoro-2-methoxypyridine boronic acid (commercially available from Asymchem)(0.5115 g, 2.992 mmol) and potassium carbonate (0.8279 g, 5.990 mmol) followed by tetrakis(triphenylphosphine)palladium (0.2374 g, 0.2054 mmol). The mixture was heated to 90 °C. After 2 hours, LCMS-showed the reaction was complete. The mixture was cooled to room temperature and then diluted with water. After extracting three times with EtOAc, the mixture was concentrated in vacuo and then purified on silica gel (0%-20% EtOAc/hexane) to afford **83.34A** (601.2 mg, 80% yield). MS ESI (pos.) m/e: 376.1 (M+H)⁺.



[01368] (5-((1S)-2,2-Dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methanol or (5-((1R)-2,2-dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methanol (**83.34B**). To a cooled solution of **83.34A** (0.6012 g, 1.601 mmol) in dry THF (15 mL) at 0 °C was added LAH (1.0M in THF)(3.2 mL, 3.2 mmol) dropwise. Upon complete addition, the reaction was maintained at 0°C and was monitored by TLC and LCMS. After 45 minutes, 1N NaOH was added to quench the reaction. Gas evolved. The resulting solution was extracted three times with EtOAc. After drying over anhydrous magnesium sulfate, filtration, and concentration, the residue was purified on silica gel (0%-20% EtOAc/hexane) to afford **83.34B** (449.9 mg, 81% yield). MS ESI (pos.) m/e: 348.1 (M+H)⁺.

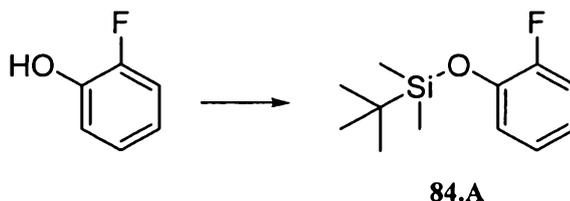


[01369] 4-(4-(Chloromethyl)-2-((1S)-2,2-dimethylcyclopentyl)-5-fluorophenyl)-5-fluoro-2-(methoxy)pyridine or 4-(4-(chloromethyl)-2-((1R)-2,2-dimethylcyclopentyl)-5-fluorophenyl)-5-fluoro-2-(methoxy)pyridine (**83.34C**). To a solution of **83.34B** (0.4463 g, 1.285 mmol) in dry DCM (17 mL) and dry DMF (0.12 mL) was added thionyl chloride (0.19 mL, 2.605 mmol) at 0 °C. The resulting solution was warmed to room temperature and monitored with TLC and LCMS. After 1.5 hours, the reaction was concentrated. The residue was diluted with EtOAc and washed once with saturated aqueous NaHCO₃ solution and once with brine. The organic layer was subsequently dried over anhydrous sodium sulfate, filtered, concentrated, and purified by silica gel flash chromatography (0-15% EtOAc/hexane) to afford **83.34C** (446.9 mg, 95% yield). MS ESI (pos.) m/e: 366.1 (M+H)⁺.

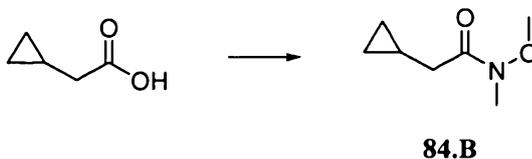
[01370] (3S)-3-Cyclopropyl-3-(3-(((5-((1S)-2,2-dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((5-((1R)-2,2-dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((5-((1S)-2,2-dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((5-((1R)-2,2-dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)propanoic acid (83.34). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 83B and 83.34C derived from 66.44AD, described herein) to yield 83.34. MS ESI (pos.) m/e: 554.2 (M+H)⁺. MS ESI (neg.) m/e: 552.1 (M-H)⁻.

[01371] **Example 84**

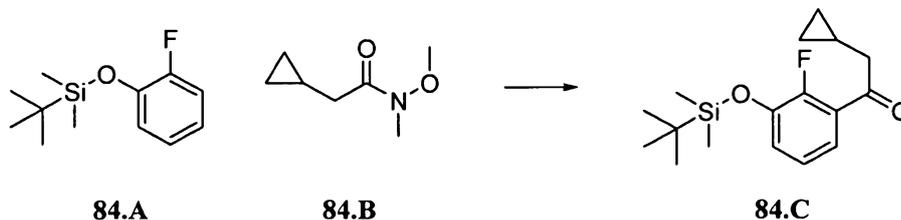
[01372] **Synthesis of (R)-methyl 4-cyclopropyl-3-(2-fluoro-3-hydroxyphenyl)butanoate and (S)-methyl 4-cyclopropyl-3-(2-fluoro-3-hydroxyphenyl)butanoate (84.F and 84.G).**



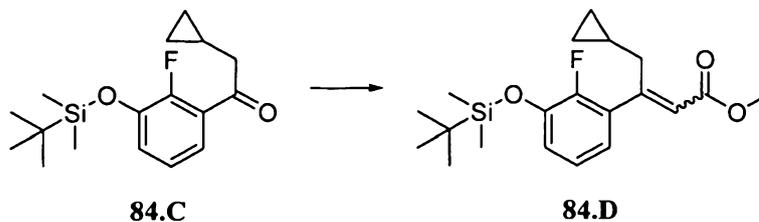
[01373] **tert-Butyl(2-fluorophenoxy)dimethylsilane (84.A).** A 500 mL round bottom flask was charged with tert-butyldimethylchlorosilane (73.9 g, 491 mmol) (available from Aldrich), DMF (220 mL), 2-fluorophenol (41.3 mL, 446 mmol) (available from Aldrich), and imidazole (75.9 g, 1115 mmol). The pale yellow solution was stirred for 1.5 hours at 25°C and diluted with hexanes (1 L). The organic phase was washed with water (1 x 300 mL), saturated aqueous NaHCO₃ (3 x 300 mL), water (3 x 300 mL) and brine (1 x 300 mL). The organic phase was then dried (MgSO₄), and concentrated to afford 84.A (101 g, 100% yield) as a colorless liquid. The crude product was used without further purification.



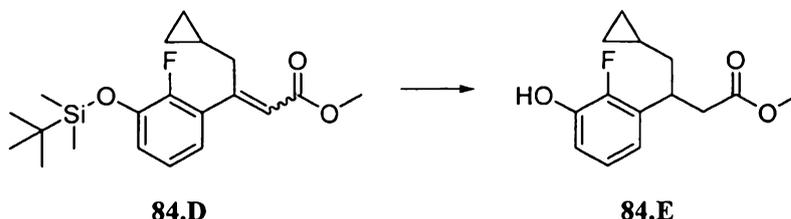
[01374] **2-Cyclopropyl-N-methoxy-N-methylacetamide (84.B).** A 500 mL round bottom flask was charged with cyclopropylacetic acid (9.87 g, 98.6 mmol) (available from Oakwood) and DCM (200 mL). To the stirred solution was added 1,1'-carbonyldiimidazole (19.2 g, 118 mmol) portionwise (vigorous gas evolution). The yellow solution was stirred for 30 minutes at room temperature, and to it was added N,O-dimethylhydroxylamine hydrochloride (11.5 g, 118 mmol) (available from Aldrich) in one portion. The heterogeneous, white mixture was stirred overnight and diluted with ether (300 mL). The organics were washed with 1 N HCl (2 x 150 mL), saturated aqueous NaHCO₃ (2 x 150 mL) and brine (1 x 150 mL), dried (MgSO₄), and concentrated to afford **84.B** (11.9 g, 84.3% yield) as a colorless liquid. The crude product was used without further purification.



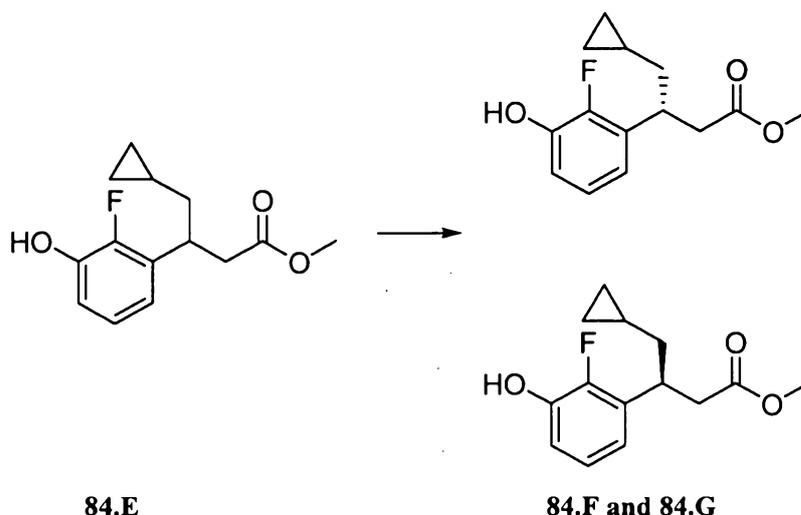
[01375] **1-(3-(tert-Butyldimethylsilyloxy)-2-fluorophenyl)-2-cyclopropylethanone (84.C).** A 1 L round bottom flask was charged with **84.A** (17.0 mL, 73.0 mmol) and THF (70 mL) and cooled to -78°C under N₂. To the cold solution was added sec-butyllithium (1.20 M/cyclohexane) (66.3 mL, 79.6 mmol) dropwise. The mixture was stirred for 30 minutes, and to it was added a solution of **84.B** (9.31 mL, 66.3 mmol) in THF (70 mL) dropwise. The final mixture was stirred for 30 minutes at -78°C. The cooling bath was removed, and the mixture was stirred for 30 minutes at ambient temperature. The reaction was quenched with saturated aqueous NH₄Cl (70 mL) and diluted with EtOAc (100 mL). The organic phase was washed with water (100 mL), 1 N HCl (100 mL) and brine (100 mL). The organic phase was then dried (MgSO₄) and concentrated. The residue was purified by silica gel flash chromatography (2% EtOAc/hexane) to afford **84.C** (14.9 g, 73% yield) as a yellow oil.



[01376] **Methyl 3-(3-(tert-butyldimethylsilyloxy)-2-fluorophenyl)-4-cyclopropylbut-2-enoate (84.D)**. A 25 mL round bottom flask was cooled to -78°C under N_2 and charged with THF (2 mL) and lithium diisopropylamide (2.0 M in heptane/THF/ethylbenzene) (2.1 mL, 4.1 mmol) (available from Aldrich). To the cold, brown solution was added methyl (trimethylsilyl)acetate (0.61 mL, 3.7 mmol) (available from Aldrich) dropwise. The orange mixture was stirred for 15 minutes, and to it was added a solution of **84.C** (0.46 g, 1.5 mmol) in THF (2 mL) dropwise. The mixture was stirred for 30 minutes at -78°C , the cooling bath was removed, and the mixture was stirred for 30 minutes at ambient temperature. The reaction was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The organic phase was washed with water, 1 N HCl and brine. The organic phase was then dried (MgSO_4) and concentrated. The residue was purified by silica gel flash chromatography (0-2% EtOAc/hexane) to afford **84.D** (mixture of geometric isomers) (0.44 g, 81% yield) as a yellow oil.



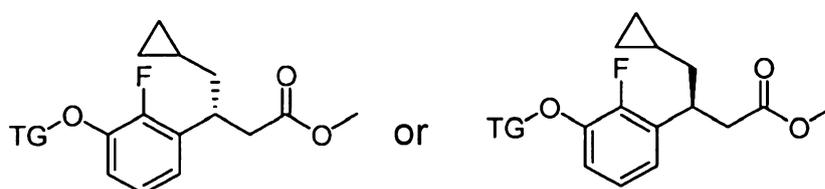
[01377] **Methyl 4-cyclopropyl-3-(2-fluoro-3-hydroxyphenyl)butanoate (84.E)**. A 250 mL round bottom flask was charged with **84.D** (4.95 g, 13.6 mmol) and MeOH (60 mL) and flushed with N_2 . To the solution were added magnesium turnings (0.990 g, 40.7 mmol) in one portion (a few turnings were fractured by hammering prior to addition to expose clean metallic edges). The gently bubbling mixture was stirred overnight at room temperature. To the mixture was added potassium fluoride (0.789 g, 13.6 mmol). The resulting mixture was stirred for 1 hour, quenched with 1 N HCl (90 mL), and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with water (2 x 50 mL) and brine (1 x 50 mL), dried (MgSO_4), and concentrated. The residue was purified by silica gel flash chromatography (0-20% EtOAc/hexane) to afford **84.E** (2.70 g, 79% yield) as a yellow oil.



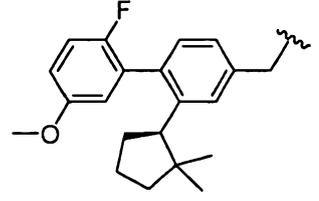
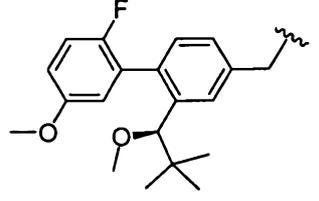
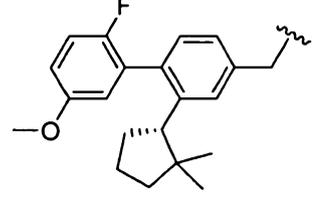
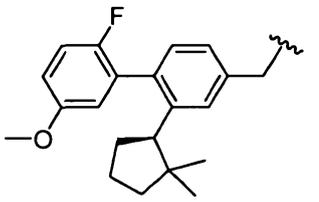
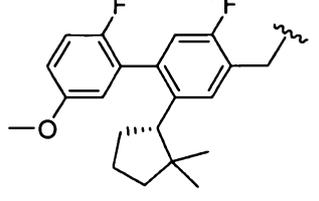
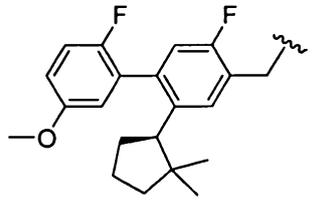
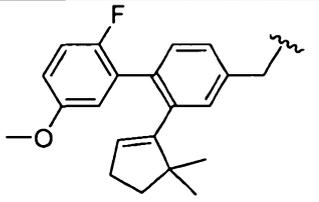
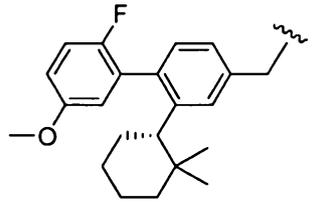
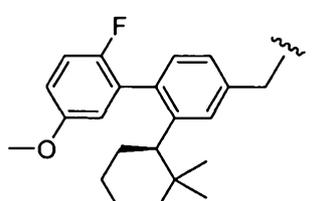
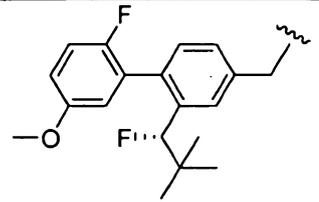
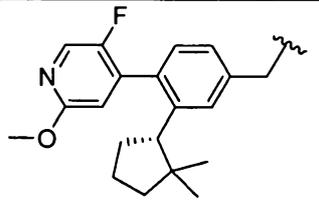
[01378] (R)-Methyl 4-cyclopropyl-3-(2-fluoro-3-hydroxyphenyl)butanoate and (S)-methyl 4-cyclopropyl-3-(2-fluoro-3-hydroxyphenyl)butanoate (**84.F** and **84.G**). Racemic **84.E** (1.97 g, 7.8 mmol) was resolved by chiral HPLC (Chiralcel OD column, 3% i-PrOH/hexanes, 220 nm, 700 mg/injection) to afford (in order of elution) **84.F** (0.98 g, 99% yield) and **84.G** (0.96 g, 97% yield) as colorless oils.

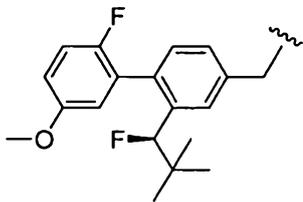
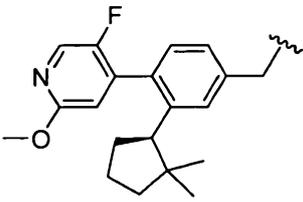
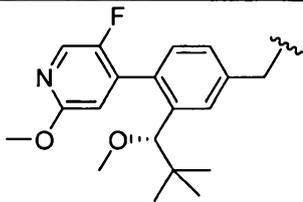
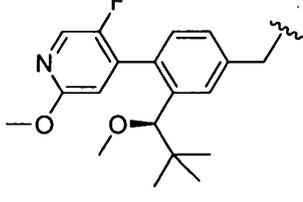
[01379] The following compounds were prepared from **84.F** and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Each of the compounds in the following table were prepared using the same enantiomer of the phenol.

Table 18



Compound	TG	Compound	TG
84.1	<p style="text-align: center;">or</p>	84.2	<p style="text-align: center;">or</p>

Compound	TG	Compound	TG
			
84.3	 <p style="text-align: center;">or</p>  <p>but not the same one as 84.1</p>	84.4	 <p style="text-align: center;">or</p> 
84.5		84.6	 <p style="text-align: center;">or</p> 
84.7		84.8	

Compound	TG	Compound	TG
	<p>or</p> 		<p>or</p> 
84.9	 <p>or</p> 		

[01380] (R)-4-Cyclopropyl-3-{3-[2-((S)-2,2-dimethyl-cyclopentyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-2-fluoro-phenyl}-butyric acid or (R)-4-cyclopropyl-3-{3-[2-((R)-2,2-dimethyl-cyclopentyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-2-fluoro-phenyl}-butyric acid or (S)-4-cyclopropyl-3-{3-[2-((S)-2,2-dimethyl-cyclopentyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-2-fluoro-phenyl}-butyric acid or (S)-4-cyclopropyl-3-{3-[2-((R)-2,2-dimethyl-cyclopentyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-2-fluoro-phenyl}-butyric acid (84.1). MS ESI (pos.) m/e: 566.3 (M+H₂O)⁺.

[01381] (R)-4-Cyclopropyl-3-{2-fluoro-3-[2'-fluoro-5'-methoxy-2-((S)-1-methoxy-2,2-dimethyl-propyl)-biphenyl-4-ylmethoxy]-phenyl}-butyric acid or (R)-4-cyclopropyl-3-{2-fluoro-3-[2'-fluoro-5'-methoxy-2-((R)-1-methoxy-2,2-dimethyl-propyl)-biphenyl-4-ylmethoxy]-phenyl}-butyric acid or (S)-4-cyclopropyl-3-{2-fluoro-3-[2'-fluoro-5'-methoxy-2-((S)-1-methoxy-2,2-dimethyl-propyl)-biphenyl-4-ylmethoxy]-phenyl}-butyric acid or (S)-4-cyclopropyl-3-{2-fluoro-3-[2'-fluoro-5'-

methoxy-2-((R)-1-methoxy-2,2-dimethyl-propyl)-biphenyl-4-ylmethoxy]-phenyl}-butyric acid (84.2). MS ESI (neg.) m/e: 551.2 (M-H)⁺.

[01382] (3R)-4-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)butanoic acid (84.3). MS ESI (pos.) m/e: 566.3 (M+H₂O)⁺.

[01383] (3R)-4-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)butanoic acid (84.4). MS ESI (neg.) m/e: 565.3 (M-H)⁺.

[01384] (3R)-4-Cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)butanoic acid (84.5). MS ESI (neg.) m/e: 545.2 (M-H)⁺.

[01385] (3R)-4-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)butanoic acid or (3S)-4-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclohexyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)butanoic acid (84.6). MS ESI (neg.) m/e: 561.3 (M-H)⁺.

[01386] (3R)-4-Cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1S)-1-fluoro-2,2-

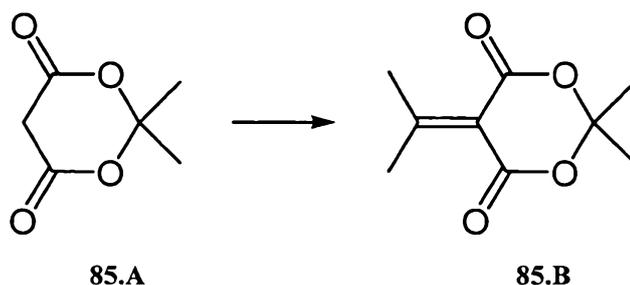
dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3R)-4-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1R)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1S)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or (3S)-4-cyclopropyl-3-(2-fluoro-3-(((2'-fluoro-2-((1R)-1-fluoro-2,2-dimethylpropyl)-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (84.7). MS ESI (neg.) m/e: 539.2 (M-H)⁺.

[01387] (3R)-4-Cyclopropyl-3-(3-(((3-((1S)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((3-((1R)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((3-((1S)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((3-((1R)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)butanoic acid (84.8). MS ESI (neg.) m/e: 548.2 (M-H)⁺.

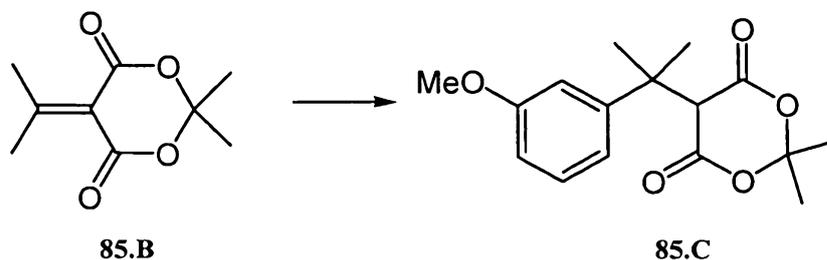
[01388] (3R)-4-Cyclopropyl-3-(3-(((3-((1S)-2,2-dimethyl-1-(methoxy)propyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((3-((1R)-2,2-dimethyl-1-(methoxy)propyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((3-((1S)-2,2-dimethyl-1-(methoxy)propyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((3-((1R)-2,2-dimethyl-1-(methoxy)propyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-2-fluorophenyl)butanoic acid (84.9). (MS ESI (pos.) m/e: 554.2 (M+H).

[01389] Example 85

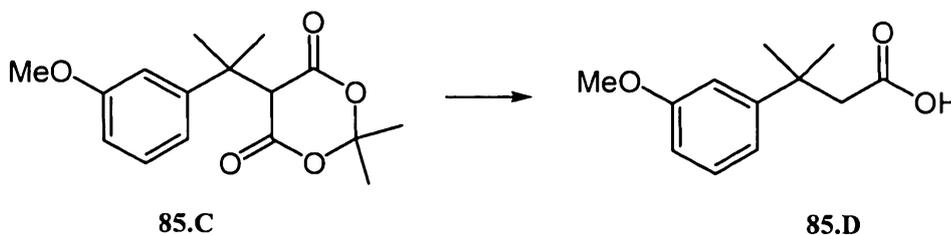
[01390] Synthesis of methyl 3-(3-hydroxyphenyl)-3-methylbutanoate (85).



[01391] **2,2-Dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (85.B).** The 2,2-dimethyl-5-(propan-2-ylidene)-1,3-dioxane-4,6-dione (**85.B**) was prepared from 2,2-dimethyl-1,3-dioxane-4,6-dione **85.A** (commercially available from Aldrich) via the same procedure described in Vogt, P.F.; et. al.; *Synthetic Communications*; **2001**, (5); pp. 679-684.

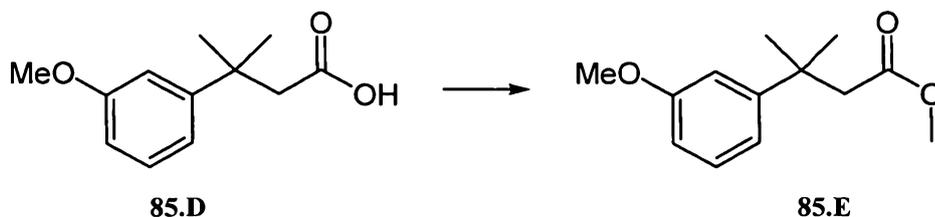


[01392] **5-(2-(3-Methoxyphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (85.C).** The 5-(2-(3-methoxyphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**85.C**) was prepared via the procedure described in Huang, X.; et. al.; *Tetrahedron Letters*; 1982, (1); pp. 75-76. from (3-methoxyphenyl)magnesium bromide (1.0 M in THF solution from Aldrich) and **85.B**. ¹H NMR (400 MHz, CDCl₃) δ ppm 7.26 (1 H, t, J=8.0 Hz), 6.94 (1 H, d, J=7.8 Hz), 6.89 (1 H, t, J=2.2 Hz), 6.79 (1 H, dd, J=8.2, 2.3 Hz), 3.81 (3 H, s), 3.62 (1 H, s), 1.67 (6 H, s), 1.66 (3 H, s), 1.34 (3 H, s).

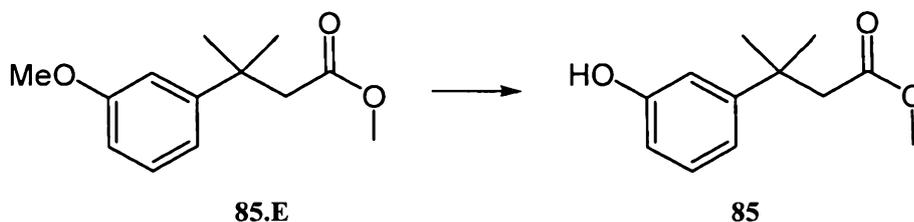


[01393] **3-(3-Methoxyphenyl)-3-methylbutanoic acid (85.D).** The 5-(2-(3-methoxyphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione **85.C** (0.313 g, 1.1 mmol) was dissolved in DMF (1.50 mL, 19 mmol). To the solution was added water (0.15 mL, 8.3 mmol). The resulting solution was then heated to 100°C and stirred for

four hours. The reaction was cooled to room temperature and then diluted with water. The mixture was extracted with EtOAc (2 x 50 mL). The combined organic layers were then washed with 1N lithium chloride solution (1 x 20 mL) and brine (1 x 20 mL) and dried over magnesium sulfate. The filtrate was then concentrated to give crude 3-(3-methoxyphenyl)-3-methylbutanoic acid **85.D** (0.247 g, 111% yield) that was used directly in the following reaction. MS ESI (pos.) m/e: 226.1 (M+H₂O)⁺.



[01394] Methyl 3-(3-methoxyphenyl)-3-methylbutanoate (85.E). 3-(3-Methoxyphenyl)-3-methylbutanoic acid **85.D** (0.22 g, 1.1 mmol) was dissolved in MeOH (11 mL) and a catalytic amount (~5 drops) of sulfuric acid was added. The solution was heated to reflux and stirred overnight. The reaction was cooled to room temperature and saturated sodium bicarbonate was added to neutralize the reaction. The mixture was then concentrated and the residue taken up in EtOAc and washed with water (2 x 30mL), 1M lithium chloride solution (1 x 30 mL) and brine (1 x 30 mL) and dried over magnesium sulfate to give the desired product methyl 3-(3-methoxyphenyl)-3-methylbutanoate **85.E** (0.227 g, 97% yield). MS ESI (pos.) m/e: 240.1 (M+H₂O)⁺.

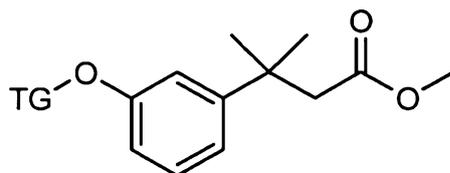


[01395] Methyl 3-(3-hydroxyphenyl)-3-methylbutanoate (85). To a solution of methyl 3-(3-methoxyphenyl)-3-methylbutanoate **85.E** (0.227 g, 1.02 mmol) in 1,2-dichloroethane (10 mL) was added 1,2-ethanedithiol (1.37 mL, 16.3 mmol) followed by aluminum chloride (1.09 g, 8.17 mmol) at 0°C. The reaction mixture was allowed to slowly warm to room temperature over four hours and was then quenched with saturated Rochelle's salt (potassium sodium tartrate) solution. The mixture was extracted (2 x 50 mL) with DCM. The combined organic layers were washed with water (1 x 40 mL) and brine (1 x 40 mL) and dried over magnesium sulfate. The filtrate was concentrated and the residue was purified by medium pressure chromatography (silica, 0 to 30% EtOAc :

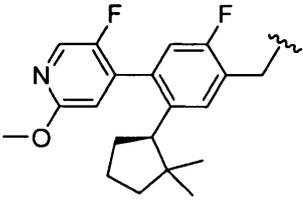
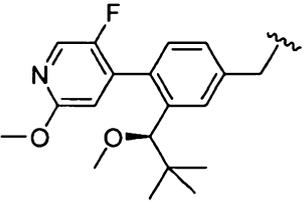
hexanes) to give methyl 3-(3-hydroxyphenyl)-3-methylbutanoate **85** (0.209 g, 98.3% yield). MS ESI (pos.) m/e: 226.0 (M+H₂O)⁺.

[01396] The following compounds were prepared from methyl 3-(3-hydroxyphenyl)-3-methylbutanoate (**85**) and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Each of the compounds in the following table were prepared using the same enantiomer of the phenol.

Table 19



Compound	TG	Compound	TG
85.1		85.2	
85.3		85.4	
	or		or
85.5		85.6	
	or		or

Compound	TG	Compound	TG
			

[01397] 3-[3-(2-tert-Butyl-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy)-phenyl]-3-methyl-butyric acid (85.1). MS ESI (pos.) m/e: 482.2 (M+H₂O)⁺.

[01398] 3-{3-[2-(5,5-Dimethyl-cyclopent-1-enyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-phenyl}-3-methyl-butyric acid (85.2). MS ESI (pos.) m/e: 520.2 (M+H₂O)⁺.

[01399] 3-(3-(((2-((1R)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-methylbutanoic acid or 3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-methylbutanoic acid (85.3). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 85 and 66.6M or 66.6N derived from peak two from the chiral separation of 66.6L from the OD-column, described herein) to yield 85.3 (0.0516 g, 84% yield over the two steps). MS ESI (neg.) m/e: 503.2 (M-H)⁺.

[01400] 3-{3-[3-((S)-2,2-Dimethyl-cyclopentyl)-4-(5-fluoro-2-methoxy-pyridin-4-yl)-benzyloxy]-phenyl}-3-methyl-butyric acid or 3-{3-[3-((R)-2,2-dimethyl-cyclopentyl)-4-(5-fluoro-2-methoxy-pyridin-4-yl)-benzyloxy]-phenyl}-3-methyl-butyric acid (85.4). MS ESI (neg.) m/e: 504.2 (M-H)⁺.

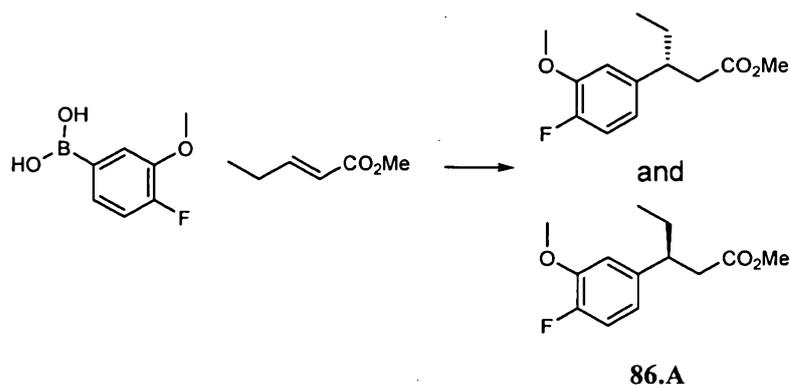
[01401] 3-(3-(((5-((1S)-2,2-Dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)phenyl)-3-methylbutanoic acid or 3-(3-(((5-((1R)-2,2-dimethylcyclopentyl)-2-fluoro-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)phenyl)-3-methylbutanoic acid (85.5). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 85 and 83.34C derived from 66.44AD, described herein) to yield 85.5. MS ESI (pos.) m/e: 524.2 (M+H)⁺. MS ESI (neg.) m/e: 522.1 (M-H)⁺.

[01402] 3-(3-(((3-((1S)-2,2-Dimethyl-1-(methoxy)propyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)phenyl)-3-methylbutanoic acid or 3-(3-

(((3-((1R)-2,2-dimethyl-1-(methoxy)propyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)phenyl)-3-methylbutanoic acid (85.6). MS ESI (pos.) m/e: 510.2 (M+H)⁺.

[01403] **Example 86**

[01404] **Synthesis of methyl (3R)-3-(4-fluoro-3-hydroxyphenyl)pentanoate (86).**



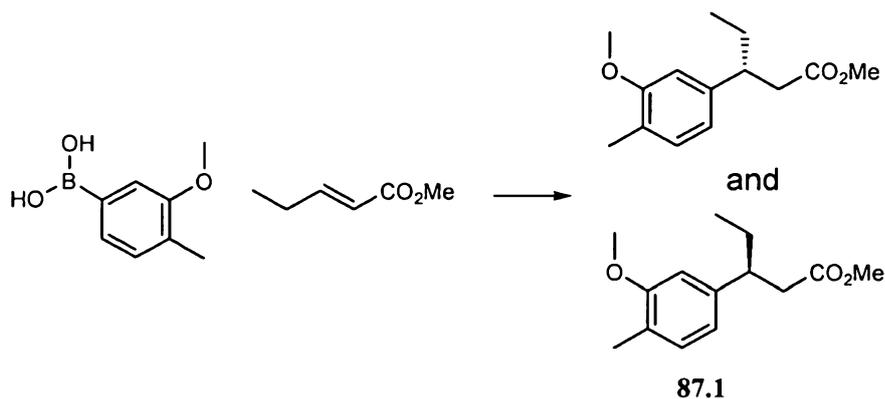
[01405] **Methyl (3R)-3-(4-fluoro-3-(methoxy)phenyl)pentanoate and methyl (3S)-3-(4-fluoro-3-(methoxy)phenyl)pentanoate (86.A).** Dioxane/water : 10/1 (22 mL) was added to a flask charged with hydroxy[(S)-BINAP]-rhodium(I) dimer (0.260 g, 0.175 mmol), and 4-fluoro-3-methoxyphenylboronic acid (3.72 g, 21.9 mmol)(commercially available from Combi-Blocks) and flushed with nitrogen and (E)-methyl pent-2-enoate (0.500 g, 4.38 mmol)(commercially available from Acros). The resulting mixture was then stirred at 40°C overnight. The reaction was diluted with EtOAc and washed with saturated sodium bicarbonate, brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography (0 to 20% EtOAc/Hexanes) to provide **86.A** (0.800 g, 76.0% yield).

Compound	TG	Compound	TG
86.1		86.2	

[01408] (3R)-3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-4-fluorophenyl)pentanoic acid or (3S)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-4-fluorophenyl)pentanoic acid (86.1). MS ESI (pos.) m/e: 519.2 (M-H).

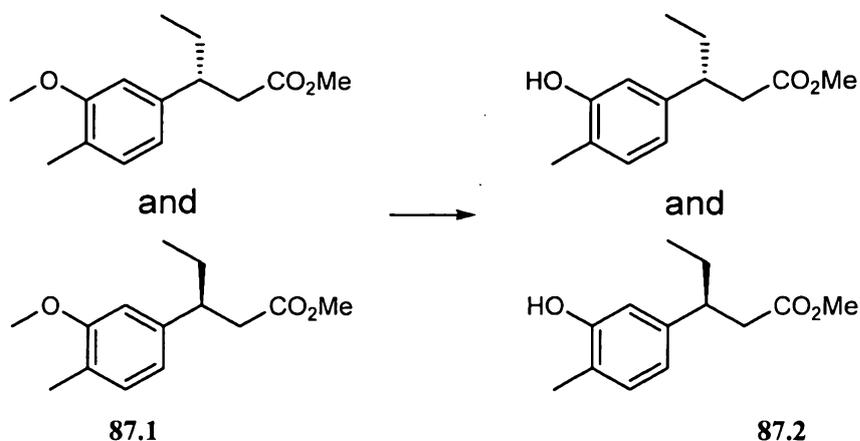
[01409] (3R)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-4-fluorophenyl)pentanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-4-fluorophenyl)pentanoic acid (86.2). MS ESI (pos.) m/e: 481.1 (M-H).

[01410] **Example 87**

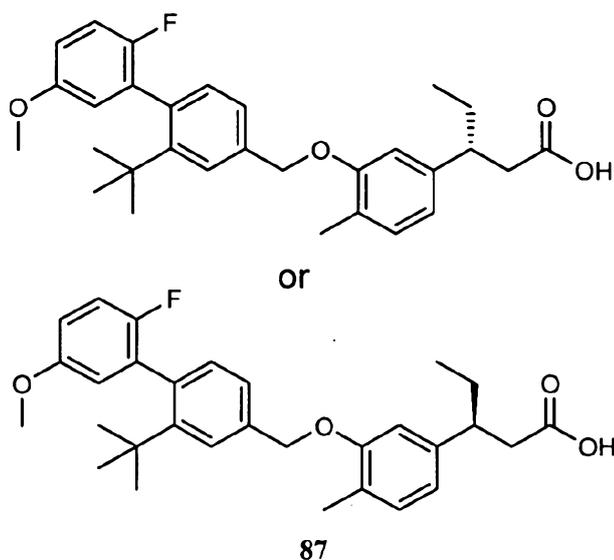


[01411] **Methyl (3R)-3-(4-methyl-3-(methoxy)phenyl)pentanoate and methyl (3S)-3-(4-methyl-3-(methoxy)phenyl)pentanoate (87.1).** Dioxane/water : 10/1 (220 mL) was added to a flask charged with hydroxy[(S)-BINAP]-rhodium(I) dimer (0.325 g, 0.219 mmol), 3-methoxy-4-methylphenylboronic acid (3.64 g, 21.9 mmol)(commercially available from Combi-Blocks) and flushed with nitrogen. Next, (E)-methyl pent-2-enoate (0.500 g, 4.38 mmol)(commercially available from Acros) was added. The resulting mixture was then stirred at 40 °C overnight. The reaction was

diluted with EtOAc and washed with saturated aqueous NaHCO₃, brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel chromatography (0 to 20% EtOAc/ Hexanes) to provide **87.1** (0.945 g, 91.3% yield).

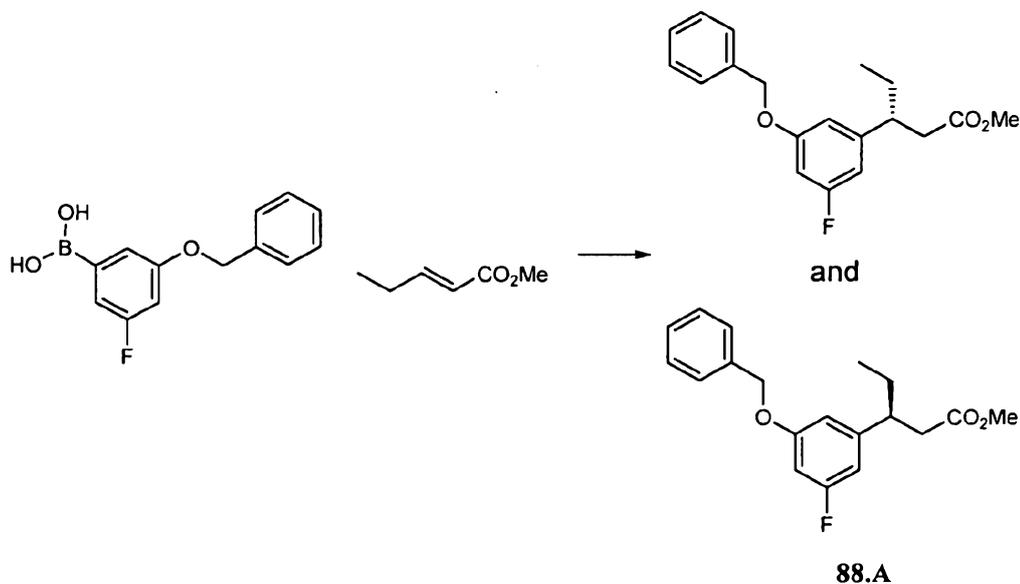


[01412] Methyl (3R)-3-(3-hydroxy-4-methylphenyl)pentanoate or methyl (3S)-3-(3-hydroxy-4-methylphenyl)pentanoate (87.2). To a solution of **87.1** (0.612 g, 2.59 mmol) in DCE (15 mL) was added 1,2-ethanedithiol (3.47 mL, 41.4 mmol) followed by aluminum chloride (1.13 mL, 20.7 mmol) at 0 °C. The reaction mixture was allowed to slowly warm to room temperature over four hours and was then quenched with saturated Rochelle's salt solution. The mixture was extracted (2 x 50 mL) with DCM. The combined organic layers were washed with water (1 x 40 mL) and brine (1 x 40 mL) and dried over magnesium sulfate. The filtrate was concentrated and the residue was purified by chromatography (silica, 0 to 30% EtOAc : hexanes) to give **87.2**. The enantiomeric excess of **87.2** was increased to >99% by purification by chiral HPLC (Chiralcel OD-H column, 3% IPA/hexane, 220 nm).



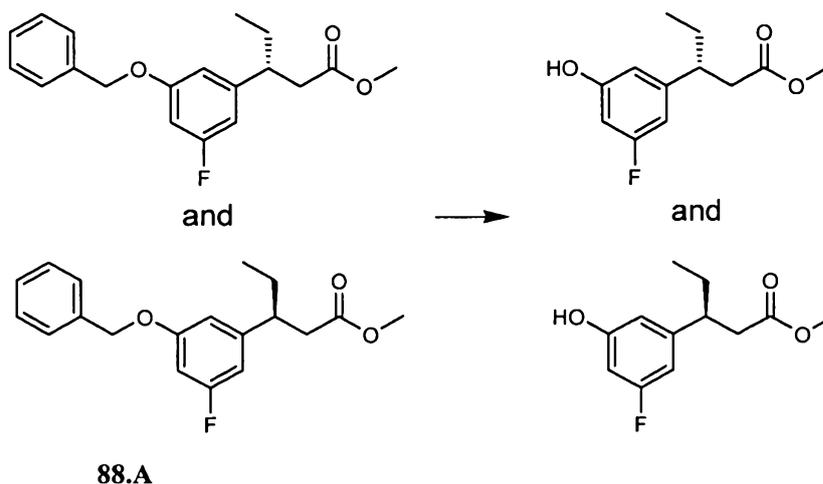
[01413] (3R)-3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-4-methylphenyl)pentanoic acid or (3S)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-4-methylphenyl)pentanoic acid (87). 87 was synthesized analogous to the method for compound 7 from 87.2 and 8.10. MS ESI (pos.) m/e: 496.3 (M+H₂O)⁺.

[01414] **Example 88**



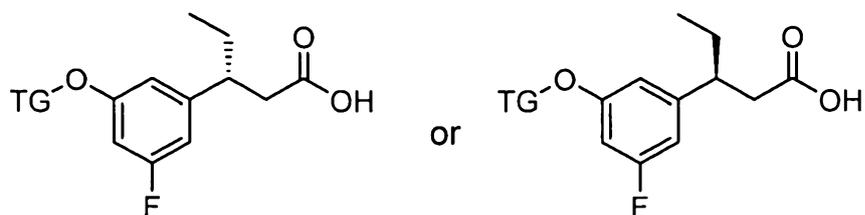
[01415] Methyl (3R)-3-(3-fluoro-5-((phenylmethyl)oxy)phenyl)pentanoate and methyl (3S)-3-(3-fluoro-5-((phenylmethyl)oxy)phenyl)pentanoate (88.A). THF (8

mL) was added to a flask charged with hydroxy[(S)-BINAP]-rhodium(I) dimer (79.2 mg, 87.6 μmol) and 3-(benzyloxy)-5-fluorophenylboronic acid (2156 mg, 8761 μmol)(commercially available from Combi-Block) and then sparged with nitrogen. To the resulting solution was added TEA (1462 μL , 10513 μmol), water (473 μL , 26283 μmol), and (E)-methyl pent-2-enoate (0.2000 g, 1752 μmol)(commercially available from Acros). The resulting mixture was then stirred at 60°C for 3 hours. After evaporation of the solvent, the residue was dissolved in EtOAc. The solution was washed with saturated aqueous sodium bicarbonate and dried over anhydrous Na_2SO_4 . Chromatography on silica gel (hexane:EtOAc 1:1) gave **88.A** (490 mg, 88.4% yield) as a colorless oil.



[01416] Methyl (3R)-3-(3-fluoro-5-hydroxyphenyl)pentanoate and methyl (3S)-3-(3-fluoro-5-hydroxyphenyl)pentanoate (**88**). To a flask containing **88.A** (490 mg, 1549 μmol) under N_2 gas was added 10% Pd/C (100 mg, 940 μmol) and sealed with a rubber septum. To this system was added EtOAc (5 mL) then vacuum was applied followed by H_2 gas (3X) then left over a balloon of H_2 overnight. The reaction was filtered, concentrated, and purified by silica gel chromatography (0 to 20% EtOAc/hexanes) to afford **88** (330 mg, 94.2% yield). The enantiomeric excess of **88** was increased to >99% by purification by chiral HPLC (Chiralcel OD-H column, 3% IPA/hexane, 220 nm).

[01417] The following compounds were prepared from **88** and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Each of the compounds in the following table were prepared using the same enantiomer of the phenol.

Table 21

Compound	TG	Compound	TG
88.1	 or 	88.2	
88.3	 or 	88.4	 or

[01418] (3R)-3-(3-(((2-((1S)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-fluorophenyl)pentanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-fluorophenyl)pentanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-

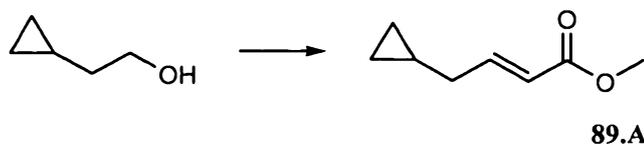
fluorophenyl)pentanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-fluorophenyl)pentanoic acid (88.1). Example 88.1 was synthesized analogous to the method for compound 7 from 88 and 66.6O. MS ESI (pos.) m/e: 521.2 (M-H).

[01419] (3R)-3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-fluorophenyl)pentanoic acid or (3S)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-fluorophenyl)pentanoic acid (88.2). Example 88.2 was synthesized analogous to the method for compound 7 from 88 and 14.5. MS ESI (pos.) m/e: 519.2 (M-H).

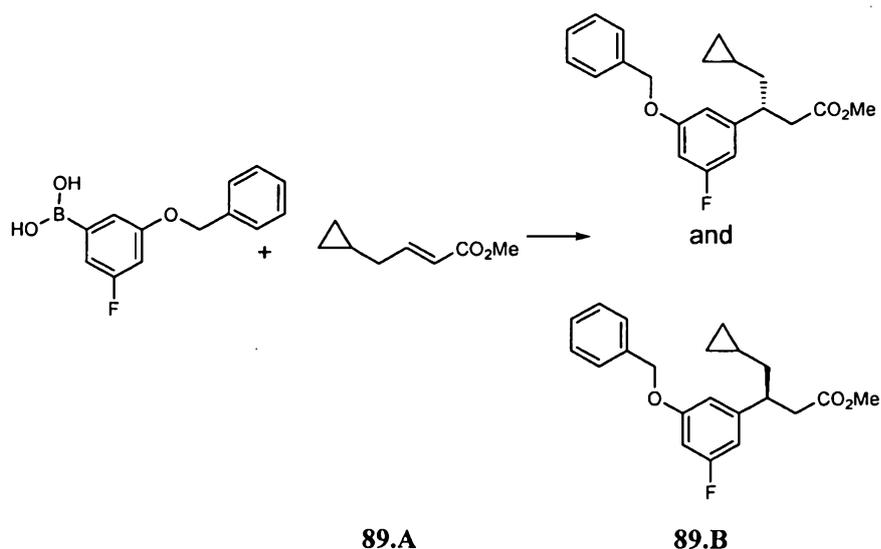
[01420] (3R)-3-(3-(((2-((1S)-2,2-Dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-fluorophenyl)pentanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-fluorophenyl)pentanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-fluorophenyl)pentanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-fluorophenyl)pentanoic acid (88.3). Example 88.3 was synthesized using a method analogous to the method used for compound 7 using 88 and 66.44D. MS ESI (pos.) m/e: 539.2 (M-H).

[01421] (3R)-3-(3-(((3-((1S)-2,2-Dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-5-fluorophenyl)pentanoic acid or (3R)-3-(3-(((3-((1R)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-5-fluorophenyl)pentanoic acid or (3S)-3-(3-(((3-((1S)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-5-fluorophenyl)pentanoic acid or (3S)-3-(3-(((3-((1R)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-5-fluorophenyl)pentanoic acid (88.4). MS ESI (pos.) m/e: 524.2 (M-H).

[01422] Example 89

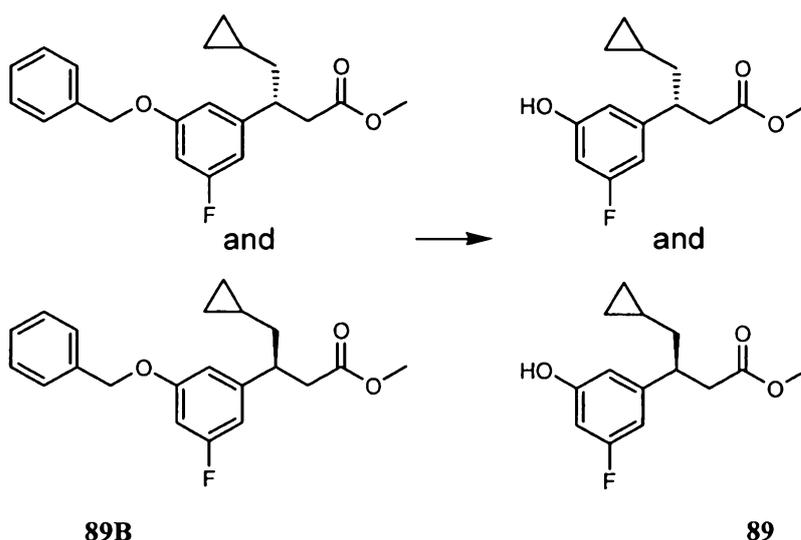


[01423] Methyl (2E)-4-cyclopropyl-2-butenoate (89.A). To a solution of 2-cyclopropylethanol (20.72 g, 240.6 mmol)(commercially available from Alfa Aesar) in 5:1 ACN/DCM (480 mL) were added TEMPO (1.879 g, 12.03 mmol)(commercially available from Aldrich) and iodobenzene diacetate (81.36 g, 252.6 mmol)(commercially available from Aldrich) as solids. The resulting slurry was stirred overnight at room temperature to afford a homogeneous solution. The reaction mixture was used directly in the next step. To a suspension of lithium chloride (15.30 g, 360.9 mmol) in ACN (400 mL) were added methyl 2-(diethoxyphosphoryl)acetate (48.04 mL, 288.7 mmol)(commercially available from Aldrich) and DBU (115.1 mL, 769.9 mmol)(commercially available from Aldrich) at room temperature. The mixture was cooled to 0°C, and to it was added 2-cyclopropylacetaldehyde (20.24 g, 240.6 mmol) solution dropwise. The resulting cloudy mixture was warmed to room temperature and stirred overnight. The mixture was partitioned between water and EtOAc. The layers were separated, and the aqueous phase was extracted with additional EtOAc. The combined organics were washed with water and brine, dried (MgSO₄), and concentrated. The crude product was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to afford **89.A** as a colorless liquid.



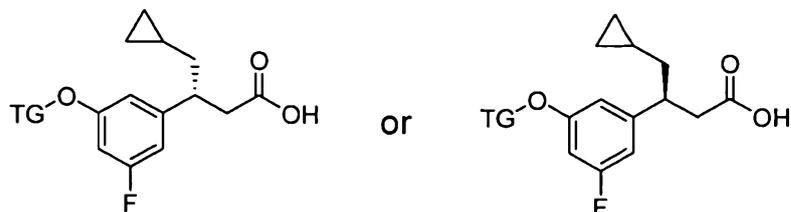
[01424] Methyl (3R)-4-cyclopropyl-3-(3-fluoro-5-((phenylmethyl)oxy)phenyl)butanoate and methyl (3S)-4-cyclopropyl-3-(3-fluoro-5-((phenylmethyl)oxy)phenyl)butanoate (89.B). THF (8 mL) was added to a flask charged with hydroxy[(S)-BINAP]-rhodium(I) dimer (64.5 mg, 71.3 μmol) and 3-

(benzyloxy)-5-fluorophenylboronic acid (1053 mg, 4280 μmol (commercially available from Combi-Blocks) and then sparged with nitrogen. To the resulting solution was added TEA (1191 μL , 8560 μmol), water (386 μL , 21401 μmol), and (E)-methyl 4-cyclopropylbut-2-enoate (200.0 mg, 1427 μmol). The resulting mixture was then stirred at 60°C for 3 hours. After removal of the solvent, the residue was dissolved in EtOAc. The solution was washed with 1 N HCl, brine, and dried over anhydrous Na_2SO_4 . Chromatography on silica gel (hexane:EtOAc 1:1) gave **89.B** (450 mg, 92.1% yield) as a colorless oil.



[01425] **Methyl (3R)-4-cyclopropyl-3-(3-fluoro-5-hydroxyphenyl)butanoate or methyl (3S)-4-cyclopropyl-3-(3-fluoro-5-hydroxyphenyl)butanoate (89).** To a flask containing **89.B** (450 mg, 1314 μmol) under N_2 gas was added 10% Pd/C (100 mg, 940 μmol), and the flask was sealed with a rubber septum. To this system was added EtOAc (20 mL). A vacuum was applied followed by H_2 gas and the process was repeated three times. The reaction was then left under a balloon of H_2 overnight. The reaction was filtered, concentrated, and purified by combiflash (0 to 20% EtOAc/hexanes) and then purified by Chiral HPLC on an OD column (3% IPA/Hexane) to afford a **89** (280 mg, 84.4% yield).

[01426] The following compounds were prepared from **89** and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Each of the compounds in the following table were prepared using the same enantiomer of the phenol.

Table 22

Compound	TG	Compound	TG
89.1	 or 	89.2	
89.3	 or 	89.4	 or

[01427] (3R)-4-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-fluorophenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-fluorophenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-

biphenyl-4-yl)methyl)oxy)-5-fluorophenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-fluorophenyl)butanoic acid (89.1). MS ESI (pos.) m/e: 547.3 (M-H).

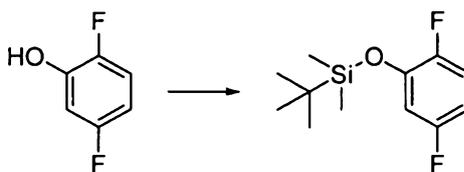
[01428] (3R)-4-Cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-fluorophenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-fluorophenyl)butanoic acid (89.2). MS ESI (pos.) m/e: 545.2 (M-H).

[01429] (3R)-4-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-fluorophenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-fluorophenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-fluorophenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2',5-difluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-fluorophenyl)butanoic acid (89.3). MS ESI (pos.) m/e: 565.3 (M-H).

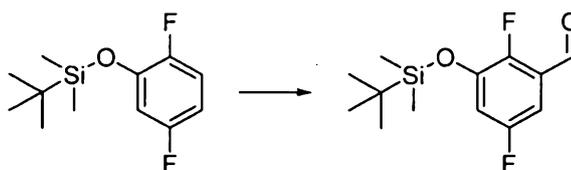
[01430] (3R)-4-Cyclopropyl-3-(3-(((3-((1S)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-5-fluorophenyl)butanoic acid or (3R)-4-cyclopropyl-3-(3-(((3-((1R)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-5-fluorophenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((3-((1S)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-5-fluorophenyl)butanoic acid or (3S)-4-cyclopropyl-3-(3-(((3-((1R)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methoxy)-4-pyridinyl)phenyl)methyl)oxy)-5-fluorophenyl)butanoic acid (89.4). MS ESI (pos.) m/e: 550.3 (M-H).

[01431] Example 90

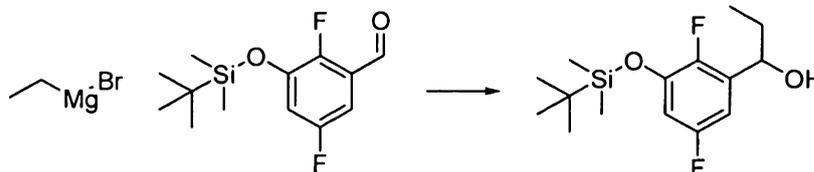
[01432] Synthesis of (R)-methyl 3-(2,5-difluoro-3-hydroxyphenyl)pentanoate (90.I) and (S)-methyl 3-(2,5-difluoro-3-hydroxyphenyl)pentanoate (90.H).

**90.A**

[01433] **tert-Butyl(2,5-difluorophenoxy)dimethylsilane (90.A).** 90.A was prepared from 2,5-difluorophenol (commercially available from Aldrich) according to the analogous method described in Example 84.

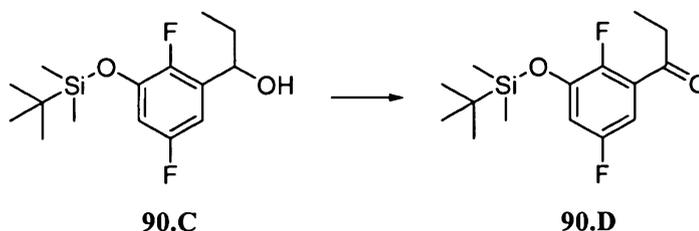
**90.A****90.B**

[01434] **3-(tert-Butyl dimethylsilyloxy)-2,5-difluorobenzaldehyde (90.B).** A 500 mL round bottom flask was charged with 90.A (8.60 g, 35.2 mmol) and THF (70 mL) and cooled to -78°C under N_2 . To the cold solution was added sec-butyllithium (1.4 M in cyclohexane) (available from Aldrich) (27.7 mL, 38.7 mmol) dropwise. The mixture was stirred for 30 minutes, and to it was added DMF (4.09 mL, 52.8 mmol) dropwise. The mixture was stirred for 30 minutes at -78°C , warmed to room temperature over 30 minutes, quenched with 1 N HCl, and diluted with EtOAc. The organic layers were washed with water and brine, dried (MgSO_4), and concentrated. The crude product was purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford 90.B (5.71 g, 59.6% yield) as a colorless oil.

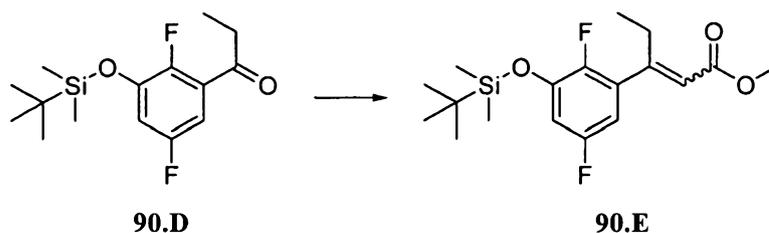
**90.B****90.C**

[01435] **1-(3-(tert-Butyl dimethylsilyloxy)-2,5-difluorophenyl)propan-1-ol (90.C).** A 200 mL round bottom flask was charged with 90.B (1.38 g, 5.1 mmol) and THF (10 mL) and cooled to -78°C under N_2 . To the cold solution was added ethylmagnesium bromide (3.0 M in ether) (commercially available from Aldrich) (5.1 mL, 15 mmol) dropwise. The mixture was stirred for 30 minutes at -78°C . The cooling

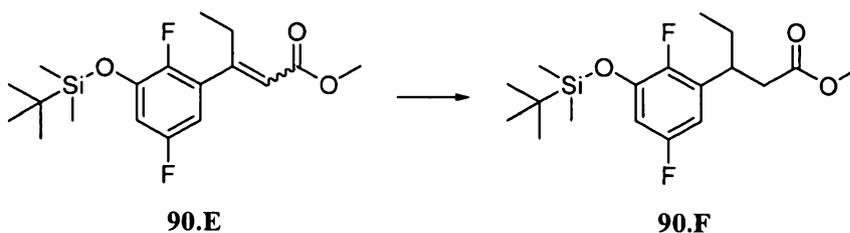
bath was removed, and the mixture was stirred for 30 minutes at ambient temperature. The reaction was quenched with saturated aqueous ammonium chloride and diluted with EtOAc. The organic layers were washed with water and brine, dried (MgSO₄), and concentrated. The crude product was purified by silica gel flash chromatography (0-15% EtOAc/hexane) to afford **90.C** (0.48 g, 31% yield) as a colorless oil.



[01436] **1-(3-(tert-Butyldimethylsilyloxy)-2,5-difluorophenyl)propan-1-one (90.D)**. A 200 mL round bottom flask was charged with **90.C** (0.48 g, 1.6 mmol), DCM (15 mL), iodobenzene diacetate (0.56 g, 1.7 mmol), and TEMPO (0.012 g, 0.079 mmol). The mixture was stirred overnight at room temperature and diluted with EtOAc. The organics were washed with saturated aqueous sodium thiosulfate, saturated aqueous sodium bicarbonate, and brine, dried (MgSO₄), and concentrated. The crude product was purified by silica gel flash chromatography (0-5% EtOAc/hexane) to afford **90.D** (0.45g, 94% yield) as a colorless oil.

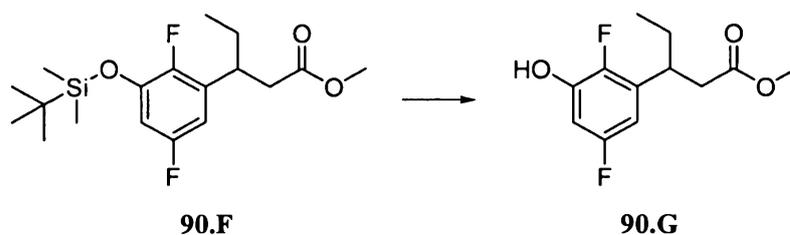


[01437] **Methyl 3-(3-(tert-butyldimethylsilyloxy)-2,5-difluorophenyl)pent-2-enoate (90.E)**. Compound **90.E** (mixture of geometric isomers) was prepared from **90.D** and methyl (trimethylsilyl)acetate (available from Aldrich) according to the analogous method described in Example 84.

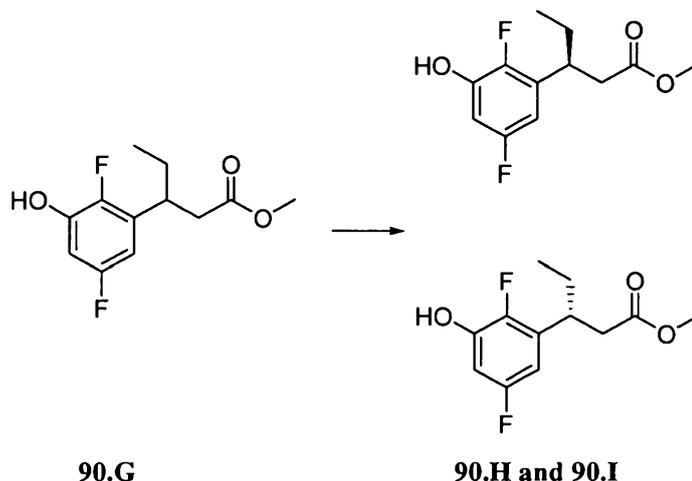


[01438] **Methyl 3-(3-(tert-butyldimethylsilyloxy)-2,5-**

difluorophenyl)pentanoate (90.F). A 75 mL pressure tube was charged with **90.E** (mixture of geometric isomers) (0.26 g, 0.73 mmol), MeOH (7 mL), and Pd/C (10 wt. %) (0.039 g, 0.036 mmol). The tube was purged 3 times with H₂ at 50 psi and sealed. The mixture was stirred for 8 hours at room temperature, filtered through silica gel (EtOAc), and concentrated to afford **90.F** (0.23 g, 88% yield) as a colorless oil. The product thus obtained was used without further purification.

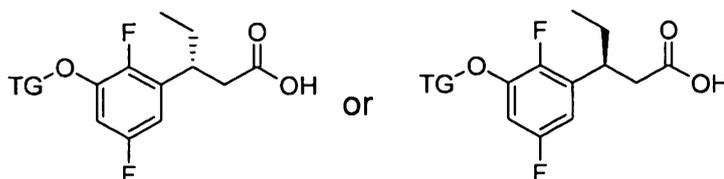


[01439] Methyl 3-(2,5-difluoro-3-hydroxyphenyl)pentanoate (90.G). A screw-cap vial was charged with **90.F** (0.23 g, 0.64 mmol), DMF (2.5 mL), and potassium fluoride (0.075 g, 1.3 mmol). The mixture was stirred for 5 minutes at room temperature, quenched with 1 N HCl, and diluted with EtOAc. The organics were washed with water and brine, dried (MgSO₄), and concentrated. The crude product was purified by silica gel flash chromatography (0-20% EtOAc/hexane) to afford **90.G** (0.13 g, 83% yield) as a colorless oil.



[01440] (S)-Methyl 3-(2,5-difluoro-3-hydroxyphenyl)pentanoate and (R)-methyl 3-(2,5-difluoro-3-hydroxyphenyl)pentanoate (90.H and 90.I). Racemic **90.G** (0.13 g, 0.53 mmol) was resolved by chiral HPLC (Chiralpak AS column, 3% IPA/hexane, detection at 220 nm) to afford (in order of elution) **90.H** (0.057 g, 88% yield, 99% e.e.) and **90.I** (0.055 g, 85% yield, 99% e.e.) as colorless oils.

[01441] The following compounds were prepared from **90.I** and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Each of the compounds in the following table were prepared using the same enantiomer of the phenol.

Table 23

Compound	TG	Compound	TG
90.1		90.2	
90.3			

[01442] (3R)-3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2,5-difluorophenyl)pentanoic acid or

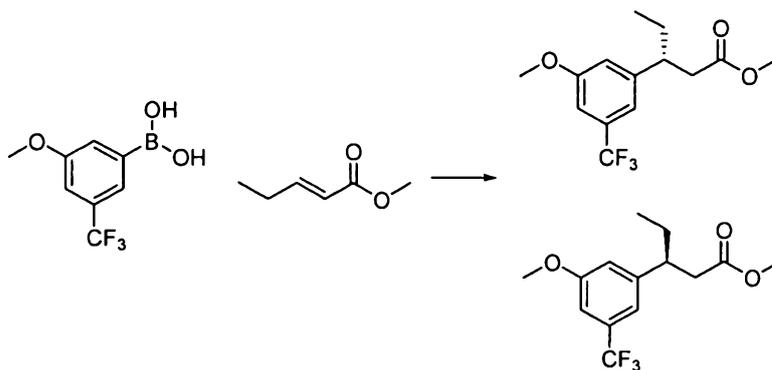
(3S)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2,5-difluorophenyl)pentanoic acid (90.1). MS ESI (neg.) m/e: 537.3 (M-H)⁺.

[01443] (3R)-3-(3-(((2-((1S)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2,5-difluorophenyl)pentanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2,5-difluorophenyl)pentanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2,5-difluorophenyl)pentanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2,5-difluorophenyl)pentanoic acid (90.2). MS ESI (neg.) m/e: 539.2 (M-H)⁺.

[01444] (3R)-3-(3-(((3-((1S)-2,2-Dimethylcyclopentyl)-4-(5-fluoro-2-(methyloxy)-4-pyridinyl)phenyl)methyl)oxy)-2,5-difluorophenyl)pentanoic acid or (3R)-3-(3-(((3-((1R)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methyloxy)-4-pyridinyl)phenyl)methyl)oxy)-2,5-difluorophenyl)pentanoic acid or (3S)-3-(3-(((3-((1S)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methyloxy)-4-pyridinyl)phenyl)methyl)oxy)-2,5-difluorophenyl)pentanoic acid or (3S)-3-(3-(((3-((1R)-2,2-dimethylcyclopentyl)-4-(5-fluoro-2-(methyloxy)-4-pyridinyl)phenyl)methyl)oxy)-2,5-difluorophenyl)pentanoic acid (90.3). MS ESI (neg.) m/e: 540.2 (M-H)⁺.

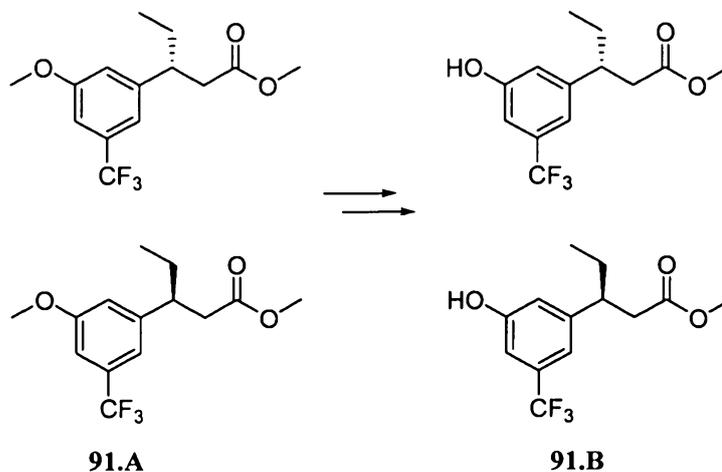
[01445] Example 91

[01446] Synthesis of (3R)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-(trifluoromethyl)phenyl)pentanoic acid or (3S)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-(trifluoromethyl)phenyl)pentanoic acid (91).



91.A

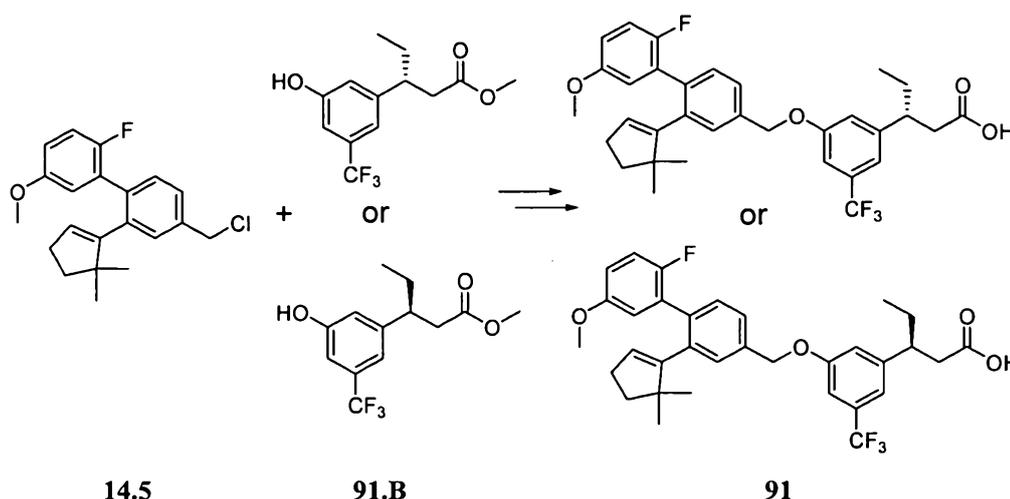
[01447] **(R)-Methyl 3-(3-methoxy-5-(trifluoromethyl)phenyl)pentanoate and (S)-methyl 3-(3-methoxy-5-(trifluoromethyl)phenyl)pentanoate (91.A).** A screw-cap vial was charged with 3-methoxy-5-(trifluoromethyl)benzeneboronic acid (available from Combi-Blocks) (0.98 g, 4.5 mmol), (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (available from Aldrich) (0.067 g, 0.11 mmol), acetylacetonatobis(ethylene)rhodium(I) (available from Ström) (0.023 g, 0.089 mmol), and 10:1 1,4-dioxane/water (3.6 mL). The mixture was purged with N₂, and to it was added methyl 2-pentenoate (available from Acros) (0.12 mL, 0.89 mmol). The resulting solution was stirred overnight at 100°C (sealed vial), cooled to room temperature, and diluted with EtOAc. The organics were washed with saturated aqueous sodium bicarbonate, water, and brine, dried (MgSO₄), and concentrated. The crude product was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to afford **91.A** (0.21 g, 81% yield, 86% e.) as a colorless liquid. The major product is believed to be the R enantiomer.



91.A

91.B

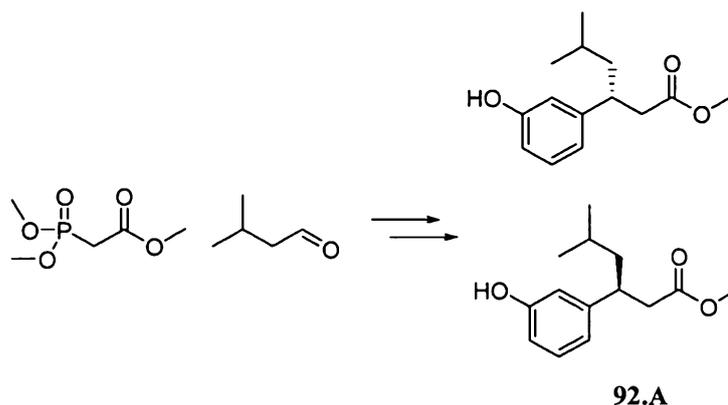
[01448] **(R)-Methyl 3-(3-hydroxy-5-(trifluoromethyl)phenyl)pentanoate or (S)-methyl 3-(3-hydroxy-5-(trifluoromethyl)phenyl)pentanoate (91.B).** 91.B (98.5% e.e.) was prepared from 91.A (86% e.e.) according to the analogous methods described in Example 77. The final chiral resolution was achieved by chiral HPLC (Chiralpak AS column, 2% IPA/hexane, detection at 220 nm) to afford 91.B as the second of two eluted peaks.



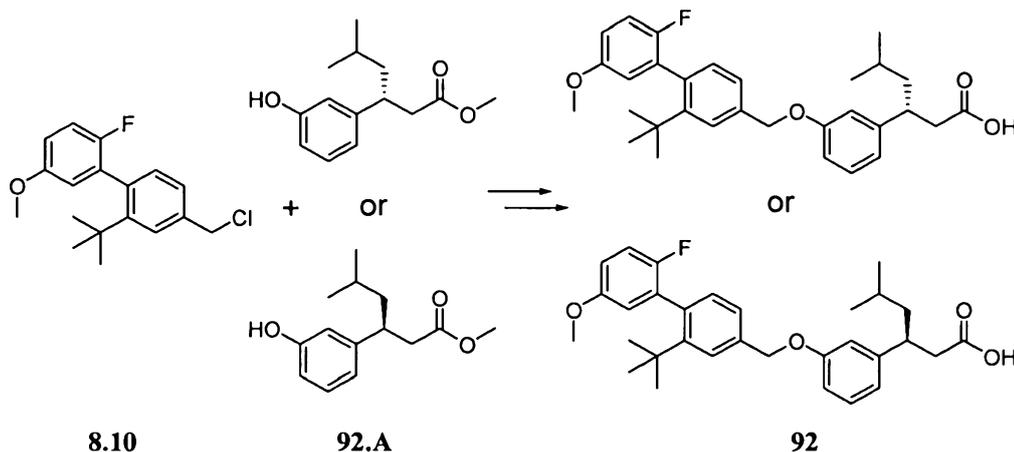
[01449] **(3R)-3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-(trifluoromethyl)phenyl)pentanoic acid or (3S)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-5-(trifluoromethyl)phenyl)pentanoic acid (91).** 91 was prepared from 91.B and 14.5 according to the analogous methods described in Example 7. MS ESI (neg.) m/e: 569.2 (M-H)⁺. The product is believed to be the R enantiomer.

[01450] **Example 92**

[01451] **Synthesis of (3R)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-5-methylhexanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-5-methylhexanoic acid (92).**



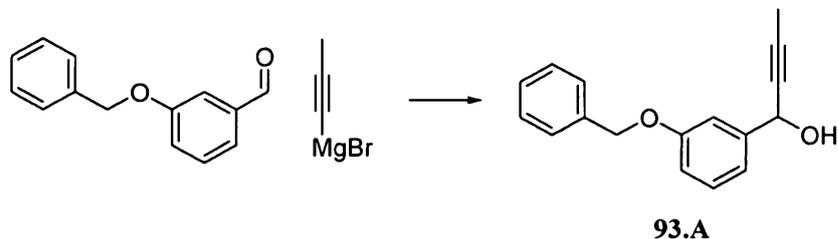
[01452] (R)-Methyl 3-(3-hydroxyphenyl)-5-methylhexanoate and (S)-methyl 3-(3-hydroxyphenyl)-5-methylhexanoate (92.A). Example 92.A (99% e.e.) was prepared from trimethyl phosphonoacetate (available from Aldrich) and isovaleraldehyde (available from Aldrich) according to the analogous methods described in Example 68. The final chiral resolution was achieved by chiral HPLC (Chiralcel OD column, 3% IPA/hexane, detection at 220 nm) to afford **92.A** as the first of two eluted peaks. The R enantiomer is believed to correspond to **92.A**.



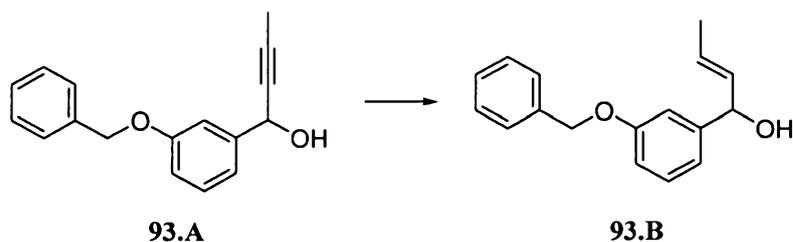
[01453] (3R)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-5-methylhexanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-5-methylhexanoic acid (92). 92 was prepared from **92.A** and **8.10** according to the analogous methods described in Example 7. MS ESI (neg.) m/e: 491.2 (M-H)⁺. The product is believed to be the R enantiomer.

[01454] Example 93

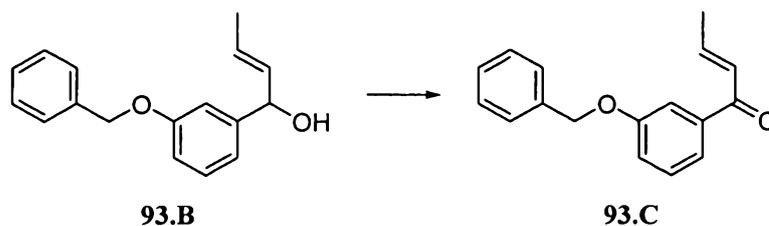
[01455] **Synthesis of (S)-ethyl 3-(3-hydroxyphenyl)-3-((1R,2R)-2-methylcyclopropyl)propanoate (93.H) and (R)-ethyl 3-(3-hydroxyphenyl)-3-((1R,2R)-2-methylcyclopropyl)propanoate (93.I).**



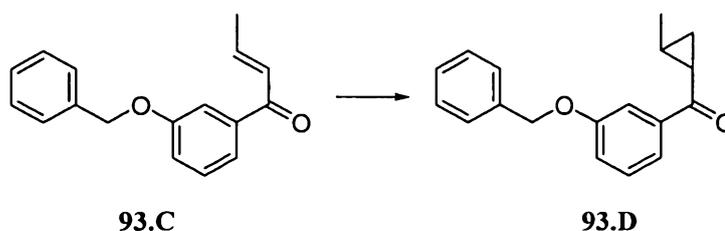
[01456] **1-(3-(Benzyloxy)phenyl)but-2-yn-1-ol (93.A).** A 1 L round bottom flask was charged with 1-propynylmagnesium bromide (0.5 M in THF) (available from Aldrich) (245 mL, 123 mmol) and cooled to -78°C . To the cold slurry was added a solution of 3-benzyloxybenzaldehyde (available from Aldrich) (20.0 g, 94.2 mmol) in THF (30 mL) over 15 minutes. The mixture was stirred for 30 minutes at -78°C , the cooling bath was removed, and stirring was continued for 1 hour at ambient temperature. The reaction was quenched with saturated aqueous ammonium chloride and diluted with EtOAc. The organics were washed with water and brine, dried (MgSO_4), and concentrated. The crude product was purified by silica gel flash chromatography (0-30% EtOAc/hexane) to afford **93.A** (23.1 g, 97% yield) as a pale yellow oil.



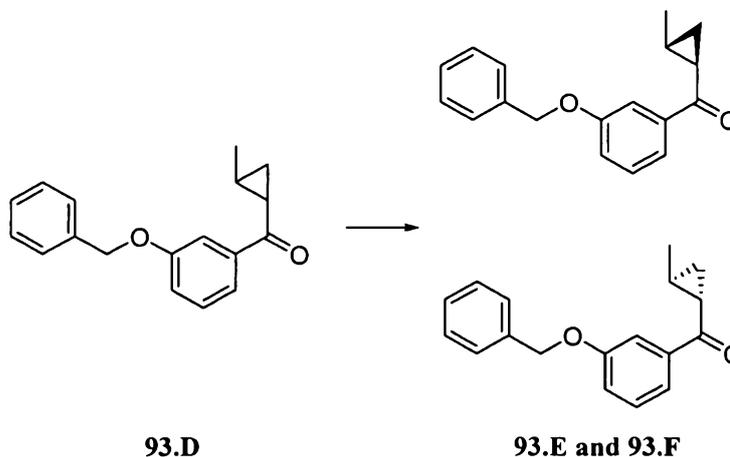
[01457] **(E)-1-(3-(Benzyloxy)phenyl)but-2-en-1-ol (93.B).** To a cold solution of sodium bis(2-methoxyethoxy)aluminum hydride (65+ wt. % in toluene) (available from Aldrich) (14.8 mL, 49.1 mmol) in ether (60 mL) was added a solution of **93.A** (6.20 g, 24.6 mmol) in ether (30 mL) dropwise under nitrogen at 0°C . The mixture was stirred for 5 minutes at 0°C , the cooling bath was removed, and stirring was continued for 3 hours at room temperature. The reaction was carefully quenched at 0°C with EtOAc, diluted with saturated aqueous Rochelle salt, and extracted with additional EtOAc. The combined organics were washed with water and brine, dried (MgSO_4), and concentrated. The crude product was purified by silica gel flash chromatography (0-20% EtOAc/hexane) to afford **93.B** (5.37 g, 86% yield) as a colorless oil.



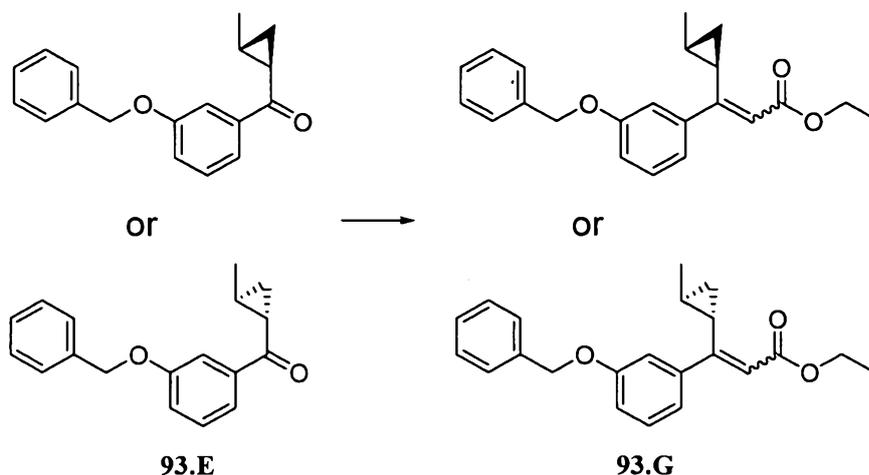
[01458] **(E)-1-(3-(Benzyloxy)phenyl)but-2-en-1-one (93.C)**. **93.C** was prepared from **93.B** via oxidation with TEMPO and iodobenzene diacetate according to the analogous method described in Example 90.



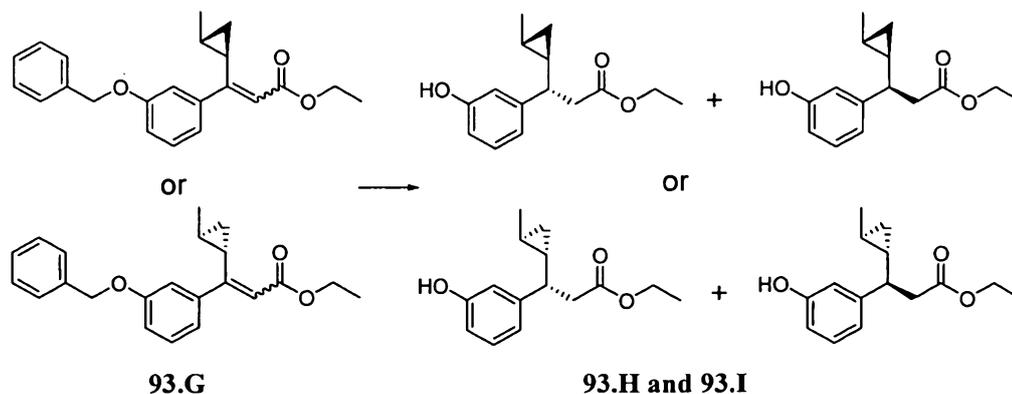
[01459] **(3-(Benzyloxy)phenyl)(2-methylcyclopropyl)methanone (93.D)**. To a solution of **93.C** (5.33 g, 21.1 mmol) in ACN (200 mL) were added trimethylsulfoxonium iodide (available from Aldrich) (5.58 g, 25.3 mmol) and DBU (4.11 mL, 27.5 mmol). The mixture was stirred overnight at 60 °C under N₂, cooled to room temperature, and concentrated. The crude product was purified by silica gel flash chromatography (0-10% EtOAc/hexane) to afford **93.D** (2.04 g, 36% yield) as a colorless oil.



[01460] **(3-(Benzyloxy)phenyl)((1R,2R)-2-methylcyclopropyl)methanone and (3-(benzyloxy)phenyl)((1S,2S)-2-methylcyclopropyl)methanone (93.E and 93.F)**. Racemic **93.D** (2.04 g, 7.66 mmol) was resolved by chiral HPLC (Chiralcel OD column, 1% IPA/hexane, detection at 220 nm) to afford (in order of elution) **93.E** (0.842 g, 82.5% yield, 99% e.e.) and **93.F** (0.864 g, 84.7% yield, 99% e.e.) as pale yellow oils.



[01461] **Ethyl 3-(3-(benzyloxy)phenyl)-3-((1R,2R)-2-methylcyclopropyl)acrylate or ethyl 3-(3-(benzyloxy)phenyl)-3-((1S,2S)-2-methylcyclopropyl)acrylate (93.G).** 93.G (mixture of geometric isomers) was prepared from 93.E and ethyl (trimethylsilyl)acetate (available from Aldrich) according to the analogous method described in Example 84.

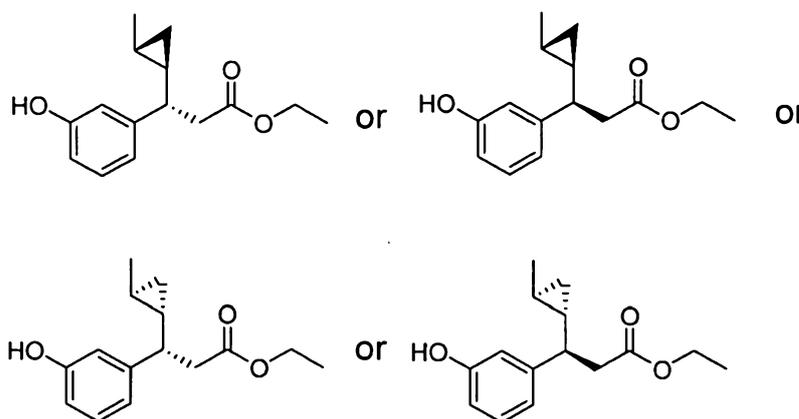


[01462] **(S)-Ethyl 3-(3-hydroxyphenyl)-3-((1R,2R)-2-methylcyclopropyl)propanoate and (R)-ethyl 3-(3-hydroxyphenyl)-3-((1R,2R)-2-methylcyclopropyl)propanoate or (R)-Ethyl 3-(3-hydroxyphenyl)-3-((1S,2S)-2-methylcyclopropyl)propanoate and (S)-ethyl 3-(3-hydroxyphenyl)-3-((1S,2S)-2-methylcyclopropyl)propanoate (93.H and 93.I).** To a solution of 93.G (0.201 g, 0.60 mmol) in EtOH (6 mL) was added platinum(IV) oxide (0.014 g, 0.060 mmol). The mixture was purged with H₂ and stirred for 48 hours under a H₂ balloon. H₂ was expelled from the mixture by purging with N₂, and Pd/C (10 wt. %) (0.032 g, 0.030 mmol) was added. The final mixture was purged with H₂, stirred for 2 hours under a H₂ balloon, filtered through silica gel (EtOAc), and concentrated. The crude product was purified by

silica gel flash chromatography (0-25% EtOAc/hexane) and subsequently by reverse-phase HPLC (40-80% ACN/water) to afford a mixture of **93.H** and **93.I**. The epimers were resolved by chiral HPLC (Chiralcel OD column, 3% IPA/hexane, detection at 220 nm) to afford (in order of elution) **93.H** (0.030 g, 20% yield, 99% d.e.) and **93.I** (0.032 g, 22% yield, 99% d.e.) as colorless oils.

[01463] The following compounds were prepared from **93.H** and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Each of the compounds in the following table were prepared using the same enantiomer of the phenol.

Table 24



Compound	TG	Compound	TG
93.1		93.2	

[01464] (3S)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-(((1R,2R)-2-methylcyclopropyl)propanoic acid or (3R)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-(((1R,2R)-2-methylcyclopropyl)propanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-(((1S,2S)-2-methylcyclopropyl)propanoic acid or (3R)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-(((1S,2S)-2-methylcyclopropyl)propanoic acid (**93.1**). MS

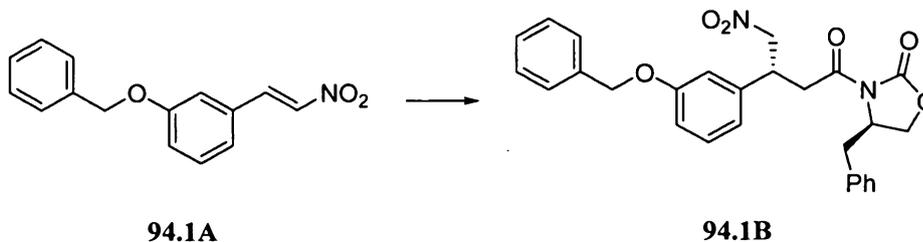
ESI (pos.) m/e: 508.3 (M+H₂O)⁺.

[01465] (3S)-3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-((1R,2R)-2-methylcyclopropyl)propanoic acid or (3R)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-((1R,2R)-2-methylcyclopropyl)propanoic acid or (3S)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-((1S,2S)-2-methylcyclopropyl)propanoic acid or (3R)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-((1S,2S)-2-methylcyclopropyl)propanoic acid (93.2). MS ESI (pos.) m/e: 546.3 (M+H₂O)⁺.

[01466] **Example 94**

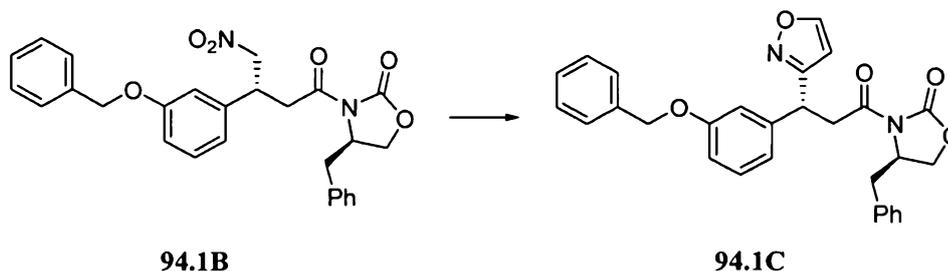
[01467] **Synthesis of methyl (3R)-3-(3-hydroxyphenyl)-3-(3-isoxazolyl)propanoate (94.1F).**

[01468] **Example 94.1**



[01469] (4R)-3-((3R)-4-Nitro-3-(3-((phenylmethyl)oxy)phenyl)butanoyl)-4-(phenylmethyl)-1,3-oxazolidin-2-one (94.1B). At -78°C, titanium(iv) chloride (1.0 M solution in DCM) (17.8 mL, 17.8 mmol) was added slowly to a solution of (R)-3-acetyl-4-benzyloxazolidin-2-one (available from Aldrich) (3.55 g, 16.2 mmol) in DCM (80 mL), followed by slow addition of diisopropylethyl amine (3.38 mL, 19.4 mmol). The mixture was stirred at -78°C for 30 minutes and then a solution of (E)-1-((3-(2-nitrovinyl)phenoxy)methyl)benzene (94.1A) (4.13 g, 16.2 mmol)(commercially available from Aldrich) in DCM (17 mL) was added dropwise (over 15 minutes). Then TiCl₄ (16 mL, 1.0 M solution in DCM) was added slowly to the reaction. The mixture was stirred at -78°C for 2 hours and then quenched with NH₄Cl solution. The mixture was extracted with EtOAc (350 mL) and the organic phase was washed with sodium bicarbonate solution and brine, dried over anhydrous Na₂SO₄. After removing solvent, the residue was recrystallized from MeOH, 94.1B (727mg), white solid was obtained. MS ESI

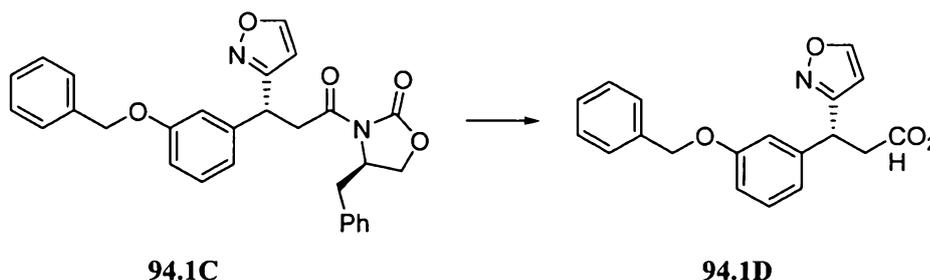
(np0s.) m/e: 475 (M+H)⁺.



[01470] **(4R)-3-((3R)-3-(3-Isoxazolyl)-3-(3-**

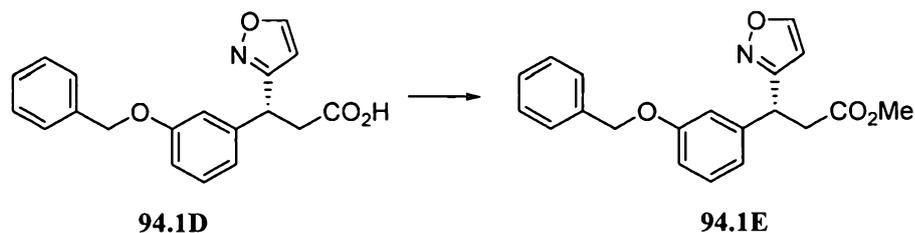
((phenylmethyl)oxy)phenyl)propanoyl)-4-(phenylmethyl)-1,3-oxazolidin-2-one

(94.1C). At room temperature, di-*t*-butyl dicarbonate (0.502 g, 2.30 mmol) was added to a solution of (R)-4-benzyl-3-((R)-3-(3-(benzyloxy)phenyl)-4-nitrobutanoyl)oxazolidin-2-one (**94.1B**) (0.727 g, 1.53 mmol), vinyl bromide, (1.0 M solution in THF (16.9 mL, 16.9 mmol), *N,N*-dimethylpyridin-4-amine (DMAP) (0.0187 g, 0.153 mmol) and TEA (0.256 mL, 1.84 mmol). The mixture was stirred at room temperature for 24 hours. The reaction was then diluted with EtOAc (200 mL) and washed with sodium bicarbonate solution and brine. The organic phase was dried over anhydrous sodium sulfate. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:2 EtOAc / hexane) and gave 558 mg of **94.1C**.

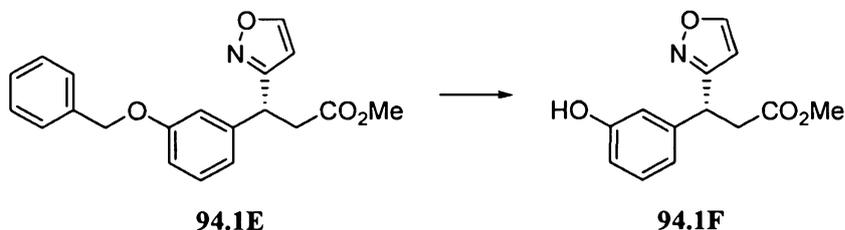


[01471] **(3R)-3-(3-Isoxazolyl)-3-(3-((phenylmethyl)oxy)phenyl)propanoic acid**

(94.1D). A solution of (R)-4-benzyl-3-((R)-3-(3-(benzyloxy)phenyl)-3-(isoxazol-3-yl)propanoyl)oxazolidin-2-one (**94.1C**) (0.558 g, 1.16 mmol) in THF (12 mL) was cooled to 0°C. H₂O₂ (30% w/w, 0.50 mL) was added, and was followed by addition of LiOH, monohydrate (0.0643 mL, 2.31 mmol) in water (4 mL). The resulting mixture was stirred at 0°C for 2 hours. The organic solvent was blown away by nitrogen, and the aqueous mixture was acidified with 1N HCl to pH 3-5. The mixture was extracted with EtOAc (100 mL). The organic phase was washed with brine, dried over anhydrous Na₂SO₄. After removing solvent, crude product (**94.1D**) (491 mg) was obtained.

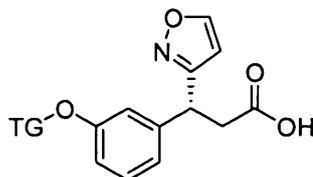


[01472] Methyl (3R)-3-(3-isoxazolyl)-3-(3-((phenylmethyl)oxy)phenyl)propanoate (**94.1E**). A mixture of (R)-3-(3-(benzyloxy)phenyl)-3-(isoxazol-3-yl)propanoic acid (**94.1D**) (0.49 g, 1.5 mmol), iodomethane (0.65 g, 4.5 mmol) and cesium carbonate (0.99 g, 3.0 mmol) in DMF (10 mL) was stirred at room temperature for 1 hour. The mixture was diluted with EtOAc (140 mL) and the organic phase was washed with water, brine and dried over anhydrous sodium sulfate. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:3 EtOAc / hexane) and gave **94.1E**, 256mg. MS ESI (neg.) m/e: 336 (M-H)⁺.



[01473] Methyl (3R)-3-(3-hydroxyphenyl)-3-(3-isoxazolyl)propanoate (**94.1F**). At 0°C, trichloroborane-dimethyl sulfide (2.0 M in DCM) (2.19 mL, 4.38 mmol) was added to a solution of (R)-methyl 3-(3-(benzyloxy)phenyl)-3-(isoxazol-3-yl)propanoate (**94.1E**) (0.246g, 0.729 mmol) in DCM (5 mL). After addition, the ice bath was removed and the mixture was stirred at room temperature for 3 hours. The flask was cooled by an ice bath and quenched by adding NaHCO₃ solution to pH 7-8. The mixture was diluted with EtOAc (120 mL), washed with brine, and dried over anhydrous sodium sulfate. After removing solvent, the residue was purified by flash chromatography (silica gel, 1:1 EtOAc / hexane) and gave **94.1F**, 122mg. MS ESI (pos.) m/e: 248 (M+H)⁺.

[01474] The compounds in the following table were prepared from methyl (3R)-3-(3-hydroxyphenyl)-3-(3-isoxazolyl)propanoate (**94.1F**) and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein.

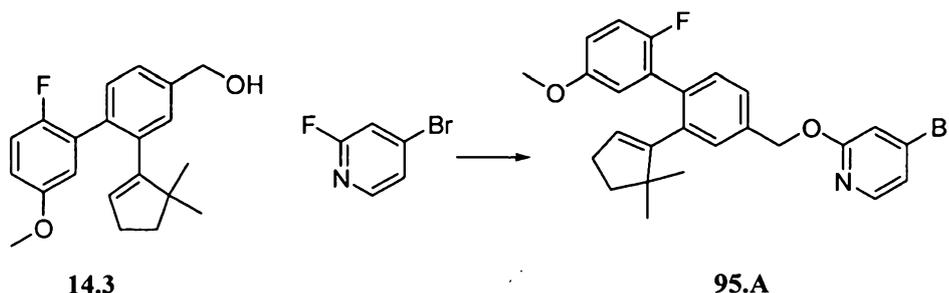
Table 25

Compound	TG	Compound	TG
94.1		94.2	

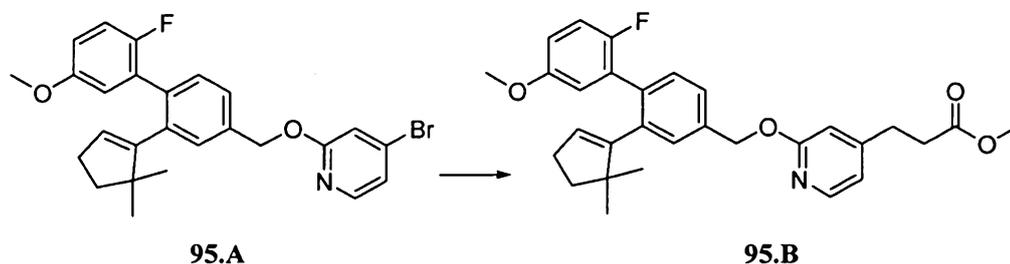
[01475] (3R)-3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-(3-isoxazolyl)propanoic acid (94.1). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 94.1F and 14.4 described herein) to yield 94.1. MS ESI (neg.) m/e: 540 (M-H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.75 (m, 1H), 7.39-7.42 (m, 1H), 7.21-7.30 (m, 3H), 7.08-7.12 (m, 1H), 6.99 (m, 1H), 6.87-6.91 (m, 3H), 6.84 (m, 1H), 6.52 (m, 1H), 5.50 (m, 1H), 5.13 (s, 2H), 4.51 (m, 1H), 3.70 (s, 3H), 3.06-3.10 (m, 1H), 2.87-2.93 (m, 1H), 2.20 (m, 2H), 1.59 (m, 2H), 0.77 (s, 6H).

[01476] (3R)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-(3-isoxazolyl)propanoic acid (94.2). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 94.1F and 8.10 described herein) to yield 94.2. MS ESI (neg.) m/e: 502 (M-H)⁺. ¹H NMR (400 MHz, DMSO-d₆) δ ppm 8.76 (m, 1H), 7.22-7.30 (m, 2H), 7.14-7.18 (m, 1H), 6.88-7.00 (m, 5H), 6.81 (m, 1H), 6.53 (m, 1H), 5.10 (s, 2H), 4.53 (m, 1H), 3.74 (s, 3H), 3.07-3.10 (m, 1H), 2.92-2.94 (m, 1H), 1.14-1.17 (m, 9H).

[01477] Example 95

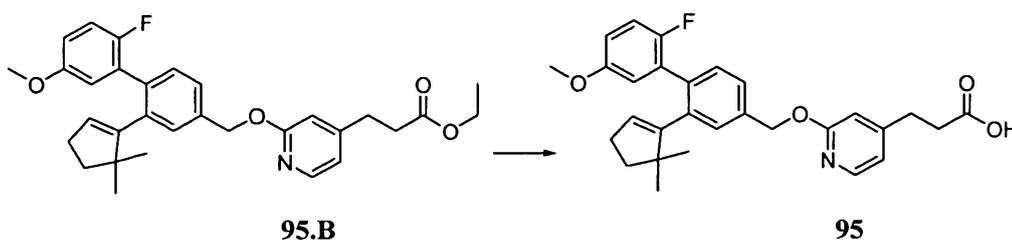


[01478] **4-Bromo-2-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)pyridine (95.A).** A dry round bottom flask containing 14.3 (0.0937 g, 0.287 mmol) in dry DMF (1 mL) was cooled in an ice bath. After 10 minutes, sodium hydride (60% wt. in oil) (15.4 mg, 0.385 mmol) was added carefully, and the mixture was stirred at 0°C. After 10 minutes, 4-bromo-2-fluoropyridine (commercially available from Synthonyx Corporation) (0.0511 g, 0.290 mmol) was added. The reaction was allowed to stir overnight at room temperature. After 18 hours, the reaction was diluted with water and extracted five times with EtOAc. The combined organic layers were then washed one time with brine and dried over anhydrous magnesium sulfate. The solid was filtered off, and the solvent was concentrated. The residue was purified by silica gel flash chromatography (0-45% EtOAc/hexane) to afford 95.A (105.9 mg, 76% yield). ¹H NMR (400 MHz) (CDCl₃) δ ppm 8.02 (1 H, d, J=4.7 Hz), 7.41 (1 H, m), 7.35 (2 H, m), 7.08 (2 H, m), 7.00 (1 H, m), 6.79 (2 H, dt, J=5.1, 2.5 Hz), 5.52 (1 H, s), 5.42 (2 H, s), 3.76 (3 H, s), 2.25 (2 H, td, J=6.9, 2.5 Hz), 1.67 (2 H, t, J=7.0 Hz), 0.87 (6 H, s).



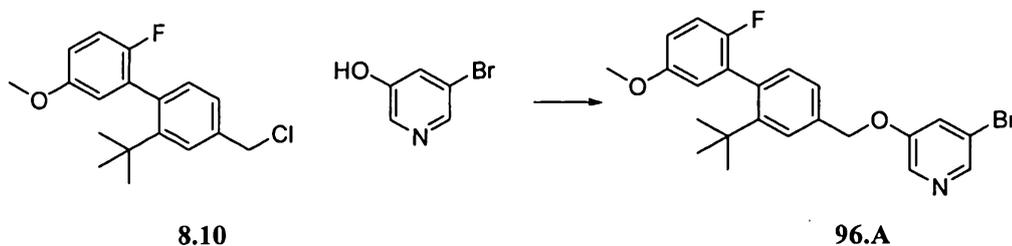
[01479] **Ethyl 3-(2-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-4-pyridinyl)propanoate (95.B).** To a sealed tube containing 95.A (0.1059 g, 0.22 mmol), bis(dibenzylideneacetone)palladium (0.0068 g, 0.012 mmol), and CTC-Q-Phos (commercially available from Strem Chemicals) (0.0079 g, 0.011 mmol) was added dry THF (2.1 mL). After 5 minutes, 3-ethoxy-3-oxopropylzinc bromide, 0.5 M solution in THF (0.9 mL, 0.45 mmol) was added

dropwise. After 1 hour, the mixture was heated to 80°C and monitored with TLC and LC-MS. After 16.5 hours, the reaction was cooled to room temperature, and then the organic solvent was removed under reduced pressure. The solid was filtered off, and the solvent was concentrated. The residue was purified by silica gel flash chromatography (0-40% EtOAc/hexane) to afford **95.B** (86.2 mg, 78% yield). ¹H NMR (500 MHz) (CDCl₃) δ ppm 8.10 (1 H, d, J=5.4 Hz), 7.41 (1 H, dd, J=7.9, 1.8 Hz), 7.33 (2 H, dd, J=4.6, 1.5 Hz), 6.98 (1 H, m), 6.81 (3 H, m), 6.70 (1 H, s), 5.52 (1 H, t, J=2.0 Hz), 5.42 (2 H, s), 4.15 (2 H, q, J=7.1 Hz), 3.76 (3 H, s), 2.93 (2 H, t, J=7.7 Hz), 2.66 (2 H, m), 2.25 (2 H, td, J=7.0, 2.4 Hz), 1.66 (2 H, t, J=7.0 Hz), 1.25 (3 H, t, J=7.1 Hz), 0.86 (6 H, s).



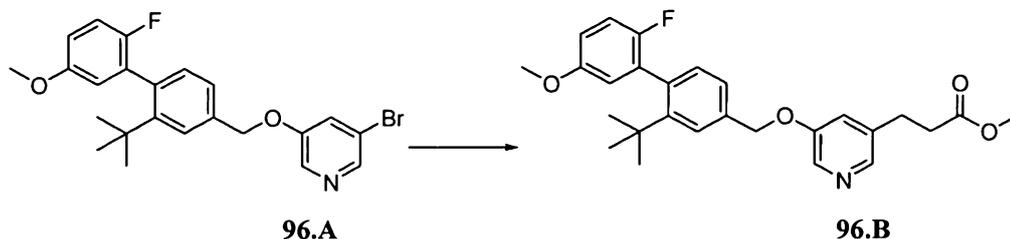
[01480] **3-(2-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-4-pyridinyl)propanoic acid (95).** The hydrolysis was conducted in an analogous manner to Example 66.6 (using **95.B** described herein) to yield **95**. ¹H NMR (400 MHz) (CDCl₃) δ ppm 8.12 (1 H, d, J=5.3 Hz), 7.44 (1 H, m), 7.36 (2 H, m), 7.00 (1 H, m), 6.82 (3 H, m), 6.71 (1 H, s), 5.54 (1 H, m), 5.40 (2 H, s), 3.76 (3 H, s), 2.94 (2 H, t, J=7.6 Hz), 2.71 (2 H, t, J=7.6 Hz), 2.25 (2 H, td, J=7.0, 2.3 Hz), 1.67 (2 H, t, J=7.0 Hz), 0.87 (6 H, s).

[01481] **Example 96**

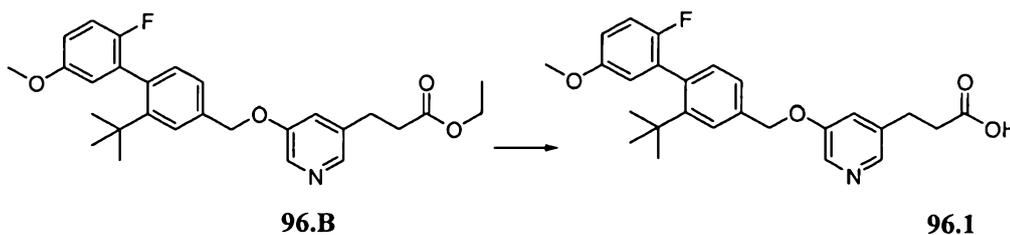


[01482] **3-Bromo-5-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)pyridine (96.A).** A dry round bottom flask containing 3-bromo-5-hydroxypyridine (0.1304 g, 0.749 mmol)(commercially available from Aldrich) in dry DMF (2 mL) was cooled in an ice bath. After 10 minutes, sodium hydride (0.0361

g, 0.903 mmol) (60% wt in oil) was added carefully, and the mixture was stirred at 0°C. After 10 minutes, **8.10** (0.2301 g, 0.750 mmol) was added. The reaction was allowed to stir overnight at room temperature. After 18 hours, the reaction was diluted with water and then extracted five times with EtOAc. The combined organic layers were then washed one time with brine and dried over anhydrous magnesium sulfate. The solid was filtered off, and the solvent was concentrated. The residue was purified by silica gel flash chromatography (0-25% EtOAc/hexane) to afford **96.A** (203.4 mg, 61% yield). ¹H NMR (400 MHz, CDCl₃) δ ppm 8.36 (2 H, dd, J=13.1, 2.2 Hz), 7.62 (1 H, d, J=1.6 Hz), 7.57 (1 H, m), 7.29 (1 H, dd, J=7.6, 1.8 Hz), 7.10 (1 H, d, J=7.4 Hz), 7.02 (1 H, t, J=8.8 Hz), 6.95 (2 H, m), 5.14 (2 H, s), 3.80 (3 H, s), 1.27 (9 H, s).



[01483] **Ethyl 3-(5-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-3-pyridinyl)propanoate (96.B)**. To a sealed tube containing **96.A** (0.2020 g, 0.455 mmol), bis(dibenzylideneacetone)palladium(0) (0.0141 g, 0.0245 mmol), and CTC-Q-Phos (0.0168g, 0.0236 mmol) was added dry THF (3 mL). After 5 minutes, 3-ethoxy-3-oxopropylzinc bromide (2.0 mL, 1.00 mmol)(0.5 M solution in THF) was added. After 1 hour, the mixture was heated to 80°C and monitored with TLC and LC-MS. After 16.5 hours, the reaction was cooled to room temperature, and the organic solvent was removed under reduced pressure. The residue was purified by silica gel flash chromatography (0-40% EtOAc/hexane) to afford **96.B** which was used without further purification (129.1 mg, 61% yield). MS ESI (pos.) m/e: 466.3 (M+H)⁺.



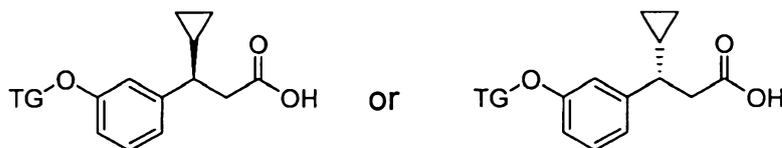
[01484] **3-(5-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-**

4-yl)methyl)oxy)-3-pyridinyl)propanoic acid (96). The hydrolysis of **96.B** was conducted in an analogous manner to Example 66.6 using **96.B** to yield **96**. MS ESI (pos.) m/e: 438.3 (M+H)⁺.

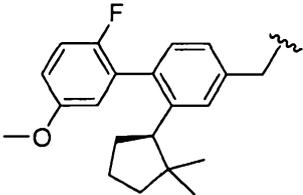
[01485] Example 97

[01486] The following compounds were prepared from (8.5) and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Each of the compounds in the following table were prepared using the same enantiomer of the phenol.

Table 26



Compound	TG	Compound	TG
97.1		97.2	
97.3			

Compound	TG	Compound	TG
	 <p>but not the same one as 97.2</p>		

[01487] (3R)-3-Cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (97.1). 97.1 was synthesized analogous to the method for compound 7 from 8.5 and 14.5. MS ESI (pos.) m/e: 513.3 (M-H).

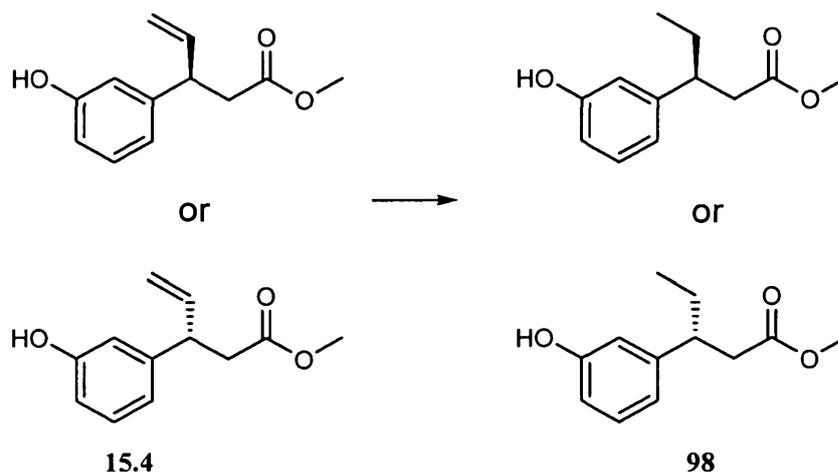
[01488] (3R)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (97.2). The alkylation and hydrolysis were conducted in an analogous manner to Example 66.6 (using 8.5 and 66.6M or 66.6N derived from peak one from the chiral separation of 66.6L from the OD-column, described herein) to yield 97.2 (0.0471 g, 81% yield over the two steps). MS ESI (neg.) m/e: 515.2 (M-H)⁺.

[01489] (3R)-3-Cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)propanoic acid (97.3). The alkylation and hydrolysis were

conducted in an analogous manner to Example 66.6 (using 8.5 and 66.6M or 66.6N derived from peak two from the chiral separation of 66.6L from the OD-column, described herein) to yield 97.3 (0.0502 g, 85% yield). MS ESI (neg.) m/e: 515.2 (M-H)⁺.

[01490] **Example 98**

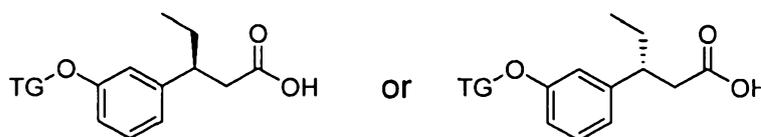
[01491] **Synthesis of methyl (3S)-3-(3-hydroxyphenyl)pentanoate (98).**

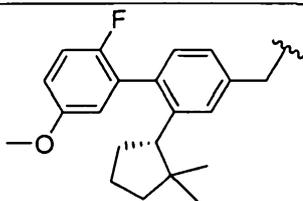
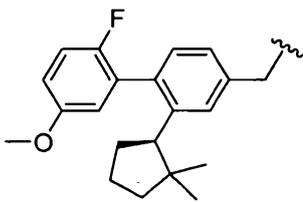
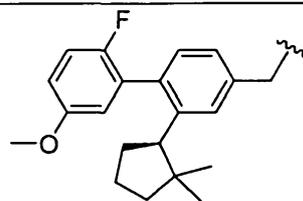
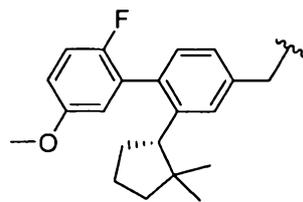


[01492] **Methyl (3S)-3-(3-hydroxyphenyl)pentanoate (98).** A 50 mL flask containing a solution of 15.4 (100 mg, 485 μ mol) in EtOAc (10 mL) was purged with N₂. To the flask was added palladium, 10 wt. % (dry), on carbon powder, wet (103 mg, 97.0 μ mol). The flask was then purged with H₂ and the contents were stirred overnight under a H₂ balloon. The black mixture was filtered through a pad of Celite and concentrated to afford a pink oil. The crude product was purified by combiflash (0 to 10% EtOAc/hexanes) yielding 98. It is believed that this is the S enantiomer.

[01493] The following compounds were prepared from 98 and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Each of the compounds in the following table were prepared using the same enantiomer of the phenol.

Table 27



Compound	TG	Compound	TG
98.1	 or 	98.2	 or  but not the same one as 98.1

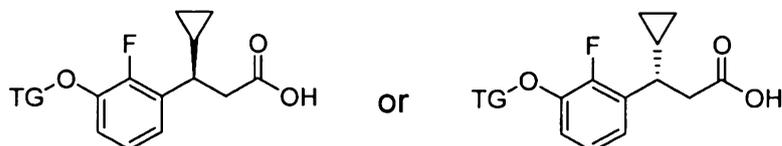
[01494] (3S)-3-(3-(((2-((1S)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3R)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid (98.1). Example 98.1 was synthesized analogous to the method for compound 7 from 98 and 66.6P. MS ESI (pos.) m/e: 503.2 (M-H).

[01495] (3S)-3-(3-(((2-((1R)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid or (3R)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)pentanoic acid (98.2). MS ESI (neg.) m/e: 503.2 (M-H)⁺.

[01496] Example 99

[01497] The following compounds were prepared from 83.C and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein. Each of the compounds in the following table were prepared using the same enantiomer of the phenol.

Table 28



Compound	TG	Compound	TG
99.1		99.2	 or
99.3	 or but not the same one as 99.2		

[01498] (3R)-3-Cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid

or (3S)-3-cyclopropyl-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid (99.1).

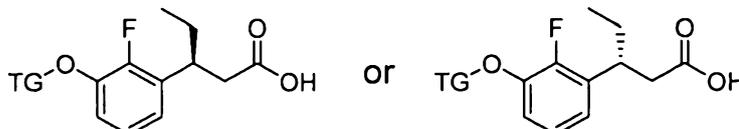
MS ESI (pos.) m/e: 550.3 (M+H₂O)⁺, 555.2 (M+Na)⁺.

[01499] (3R)-3-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid (99.2). MS ESI (pos.) m/e: 535.2 (M+H)⁺, 552.2 (M+H₂O)⁺, 557.2 (M+Na)⁺.

[01500] (3R)-3-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3R)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid or (3S)-3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)propanoic acid (99.3). MS ESI (neg.) m/e: 533.2 (M-H)⁺.

[01501] Example 100

[01502] The following compounds were prepared from 77.H and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein.

Table 29

Compound	TG	Compound	TG
100.1	 or 	100.2	 or but not the same one as 100.1

[01503] (3S)-3-(3-(((2-((1R)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3S)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3R)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid (100.1). Example 100.1 was synthesized analogous to the method for compound 7 from 77.H and 66.6P. MS ESI (pos.) m/e: 521.2 (M-H).

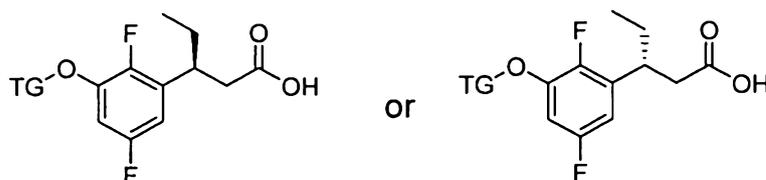
[01504] (3S)-3-(3-(((2-((1S)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3R)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-

fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2-fluorophenyl)pentanoic acid (100.2). 100.2 was synthesized analogous to the method for compound 7 from 77.H and 66.6O. MS ESI (pos.) m/e: 521.2 (M-H).

[01505] **Example 101**

[01506] The following compounds were prepared from 90.H and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein.

Table 30



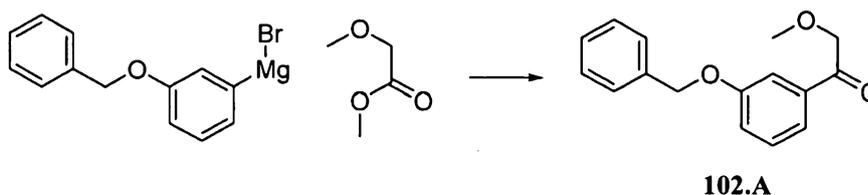
Compound	TG	Compound	TG
101.1		101.2	

[01507] **(3S)-3-(3-(((2-(5,5-Dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2,5-difluorophenyl)pentanoic acid or (3R)-3-(3-(((2-(5,5-dimethyl-1-cyclopenten-1-yl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2,5-difluorophenyl)pentanoic acid (101.1).** MS ESI (neg.) m/e: 537.3 (M-H)⁺.

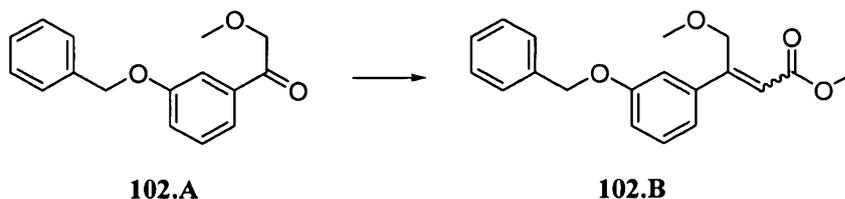
[01508] **(3S)-3-(3-(((2-((1S)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2,5-difluorophenyl)pentanoic acid or (3S)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methyloxy)-1,1'-biphenyl-**

4-yl)methyl)oxy)-2,5-difluorophenyl)pentanoic acid or (3R)-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2,5-difluorophenyl)pentanoic acid or (3R)-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)-2,5-difluorophenyl)pentanoic acid (101.2). MS ESI (neg.) m/e: 539.2 (M-H)⁺.

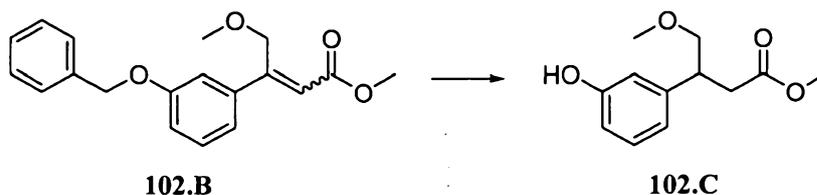
[01509] **Example 102**



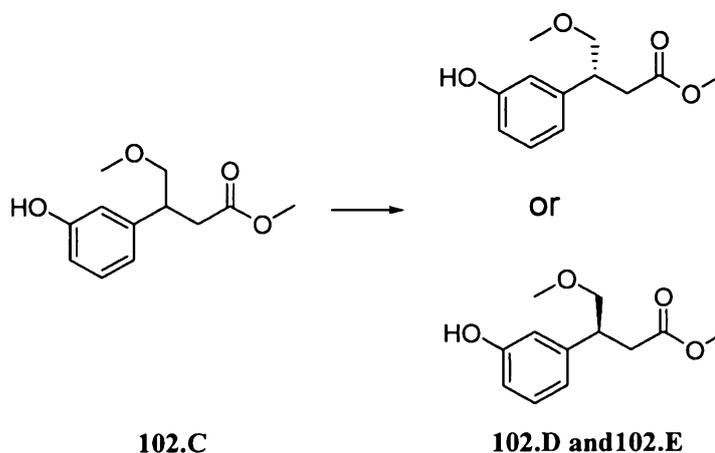
[01510] **1-(3-(Benzyloxy)phenyl)-2-methoxyethanone (102.A)**. To a solution of methyl methoxyacetate (available from Aldrich) (0.48 mL, 4.8 mmol) in ether (20 mL) was added 3-benzyloxyphenylmagnesium bromide (1.0 M in THF) (available from Aldrich) (5.0 mL, 5.0 mmol) dropwise at -78°C. The mixture was warmed to room temperature overnight, quenched with 1 N HCl, and diluted with EtOAc. The organic layers were washed with water and brine, dried (MgSO₄), and concentrated. The crude product was purified by silica gel flash chromatography (0-20% EtOAc/hexane) to afford **102.A** (0.17 g, 14% yield) as a pale yellow oil.



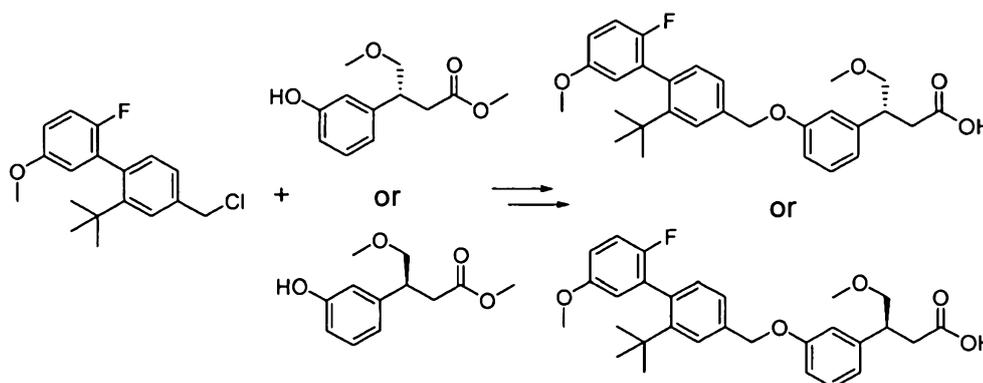
[01511] **Methyl 3-(3-(benzyloxy)phenyl)-4-methoxybut-2-enoate (102.B)**. To a solution of **102.A** (0.17 g, 0.66 mmol) in benzene (7 mL) was added methyl (triphenylphosphoranylidene)acetate (available from Aldrich) (2.2 g, 6.6 mmol) at room temperature. The mixture was stirred for 72 hours at reflux (100°C), cooled to room temperature, filtered through silica gel (EtOAc), and concentrated. The crude product was purified by silica gel flash chromatography (0-20% EtOAc/hexane) to afford **102.B** (mixture of geometric isomers) (0.11 g, 53% yield) as a pale yellow oil.



[01512] Methyl 3-(3-hydroxyphenyl)-4-methoxybutanoate (102.C). To a solution of **102.B** (mixture of geometric isomers) (0.11 g, 0.35 mmol) in EtOAc (2 mL) was added Pd/C (10 wt. %) (0.019 g, 0.018 mmol) under N₂. The mixture was purged with H₂, stirred overnight under a H₂ balloon, filtered through silica gel (EtOAc), and concentrated. The crude product was purified by silica gel flash chromatography (10-40% EtOAc/hexane) to afford **102.C** (0.060 g, 76%) as a pale yellow oil.



[01513] (R)-Methyl 3-(3-hydroxyphenyl)-4-methoxybutanoate and (S)-methyl 3-(3-hydroxyphenyl)-4-methoxybutanoate (102.D and 102.E). Racemic **102.C** (0.060 g, 0.27 mmol) was resolved by chiral HPLC (Chiralcel OD column, 3% IPA/hexane, detection at 220 nm) to afford (in order of elution) **102.D** (0.030 g, 100% yield, 99% e.e.) and **102.E** (99% e.e.) as pale yellow oils.



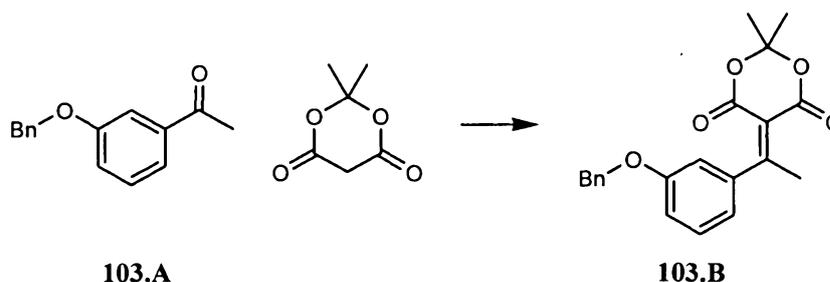
8.10

102.D

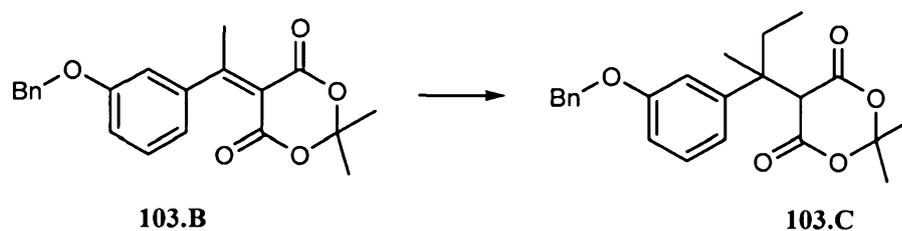
102

[01514] (3R)-3-(3-(((2-(1,1-Dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-(methoxy)butanoic acid or (3S)-3-(3-(((2-(1,1-dimethylethyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-4-(methoxy)butanoic acid (102). 102 was prepared from 102.D and 8.10 according to the analogous methods described in Example 7. MS ESI (pos.) m/e: 481.1 (M+H)⁺, 498.2 (M+H₂O)⁺, 503.2 (M+Na)⁺.

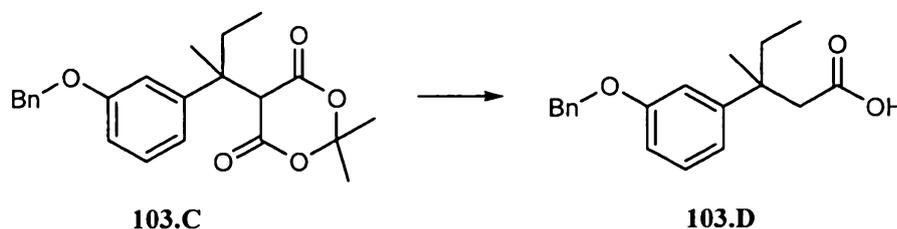
[01515] **Example 103**



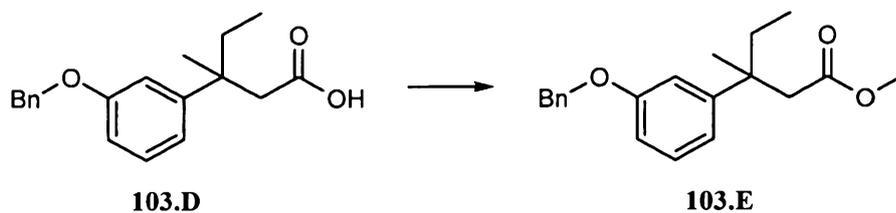
[01516] **2,2-Dimethyl-5-(1-(3-((phenylmethyl)oxy)phenyl)ethylidene)-1,3-dioxane-4,6-dione (103.B)**. A 1.0M solution of titanium tetrachloride in DCM (9.3 mL, 9.3 mmol) was injected dropwise to THF (15 mL) cooled to 0°C. A solution of 1-(3-(benzyloxy)phenyl)ethanone (1.0 g, 4.42 mmol) (commercially available from Aldrich) and 2,2-dimethyl-1,3-dioxane-4,6-dione (701 mg, 4.86 mmol) (commercially available from Aldrich) in THF (5 mL) was then injected dropwise into the flask followed by dropwise addition of pyridine (1.8 mL, 22.1 mmol). The reaction temperature was allowed to warm to room temperature and the mixture was stirred overnight. The reaction was then quenched with water, extracted with EtOAc, dried over MgSO₄, and filtered. The solvent was removed and the resulting crude mixture was purified by silica gel flash chromatography (hexane:EtOAc = 4:1 to 1:1) to afford 5-(1-(3-(benzyloxy)phenyl)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione **103.B** (855 mg, 55% yield).



[01517] **2,2-Dimethyl-5-(1-methyl-1-(3-((phenylmethyl)oxy)phenyl)propyl)-1,3-dioxane-4,6-dione (103.C)**. Into a solution of 5-(1-(3-(benzyloxy)phenyl)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione **103.B** (325 mg, 922 μmol) in anhydrous THF (2 mL) was injected ethylmagnesium bromide (769 μL , 2306 μmol) at 0°C. The reaction was stirred for 20 minutes before raising the temperature to room temperature. The reaction mixture was then stirred for 3 hours. The reaction was then quenched with 6N HCl (0.383 mL), extracted with DCM and washed with a saturated NaHCO_3 solution. The resulting crude mixture was purified by silica gel flash chromatography (hexane:EtOAc = 2:1) to afford 5-(2-(3-(benzyloxy)phenyl)butan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione **103.C** (209 mg, 59% yield).

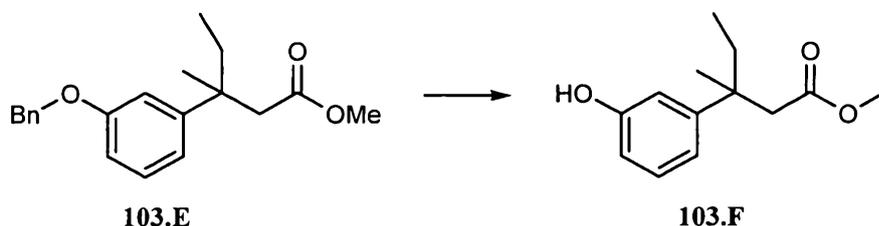


[01518] **3-Methyl-3-(3-((phenylmethyl)oxy)phenyl)pentanoic acid (103.D)**. A solution of 5-(2-(3-(benzyloxy)phenyl)butan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione **103.C** (209 mg, 546 μmol) in DMF (2 mL) and H_2O (0.2 mL) was heated to 90°C overnight. The reaction was then diluted with 0.2N HCl, extracted with EtOAc, dried over MgSO_4 , filtered, stripped, and purified by silica gel chromatography to afford 3-(3-(benzyloxy)phenyl)-3-methylpentanoic acid **103.D** (106.4 mg, 65.3% yield).

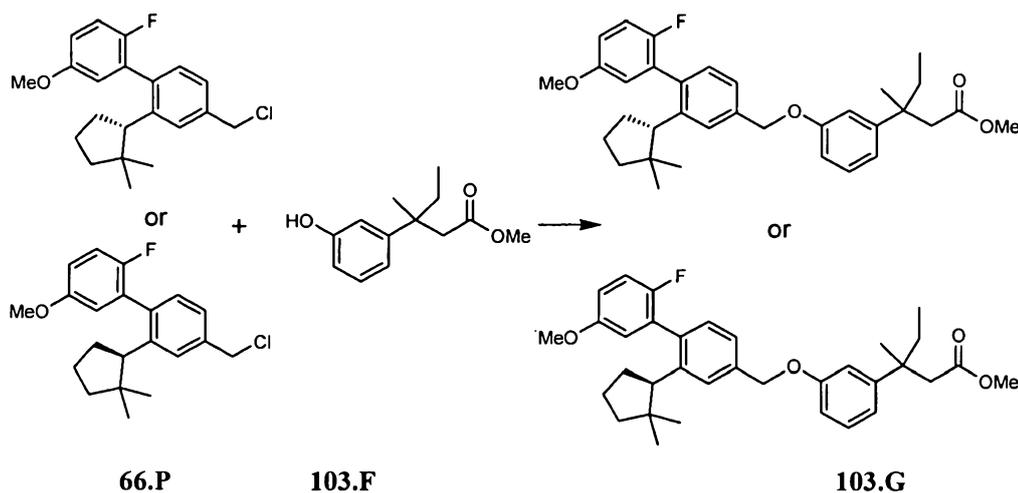


[01519] **Methyl 3-methyl-3-(3-((phenylmethyl)oxy)phenyl)pentanoate (103.E)**. Into a solution of 3-(3-(benzyloxy)phenyl)-3-methylpentanoic acid **103.D** (184 mg, 617 μmol) in MeOH (3 mL) was injected H_2SO_4 (3.29 μL , 61.7 μmol), and the mixture was heated at 60°C overnight. The reaction was quenched with saturated NaHCO_3 solution, extracted with DCM, dried over Na_2SO_4 , filtered, stripped, and

purified by silica gel chromatography to afford methyl 3-(3-(benzyloxy)phenyl)-3-methylpentanoate **103.E** (177 mg, 91.9% yield).

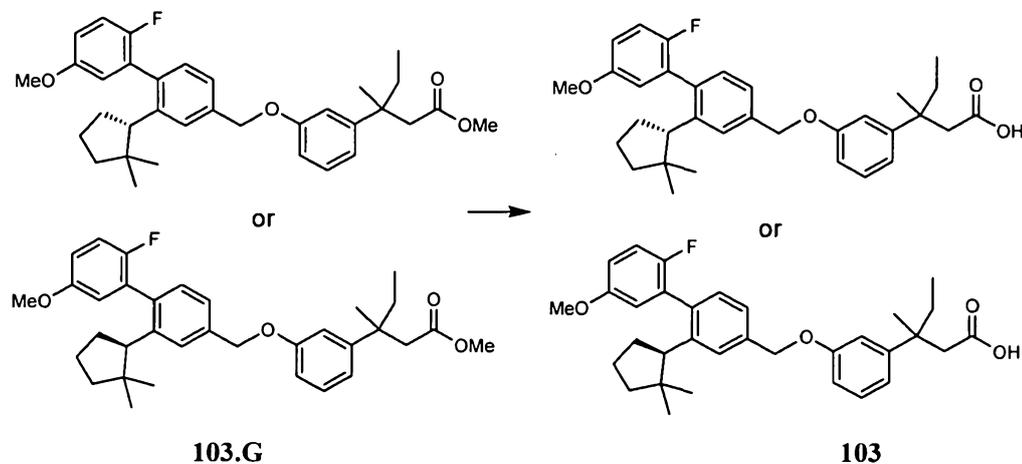


[01520] Methyl 3-(3-hydroxyphenyl)-3-methylpentanoate (103.F). Into a solution of methyl 3-(3-(benzyloxy)phenyl)-3-methylpentanoate **103.E** (100 mg, 320 μ mol) in MeOH (5 mL) was added palladium on carbon (34.1 mg, 320 μ mol). The reaction was charged with H₂ to 50 psi and stirred for 3 hours. The reaction was then filtered through Celite, washed with DCM, stripped, and purified by silica gel chromatography to afford methyl 3-(3-hydroxyphenyl)-3-methylpentanoate **103.F** (65.3 mg, 91.8% yield).

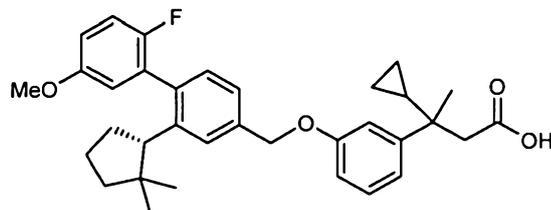


[01521] Methyl 3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-methylpentanoate or methyl 3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-methylpentanoate (103.G). Into a solution of **66.P** (102 mg, 294 μ mol) and **103.F** (65.3 mg, 294 μ mol) in DMF was added cesium carbonate (287 mg, 881 μ mol) at room temperature. The mixture was then stirred overnight at room temperature. The reaction was quenched with water, extracted with EtOAc, dried over

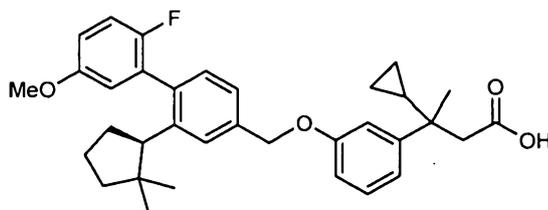
MgSO₄, filtered, stripped, and purified by silica gel chromatography to afford **103.G** (130 mg, 83% yield).



[01522] 3-(3-(((2-((1S)-2,2-Dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-methylpentanoic acid or 3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)-3-methylpentanoic acid (**103**). Into a solution of **103.G** (130 mg, 244 μ mol) in THF (2 mL) and EtOH (2 mL) was injected a 4 N solution of LiOH (610 μ L, 2440 μ mol). The reaction mixture was then stirred overnight at 50°C. The reaction was quenched with 410 μ L of 6 N HCl, and extracted with EtOAc. The organic layers were combined and dried over MgSO₄, filtered, and stripped. The crude mixture was then purified by silica gel chromatography to afford carboxylic acid **103** (100 mg, 79% yield). MS ESI (neg.) m/e: 517.3 (M-H).

[01523] Example 104

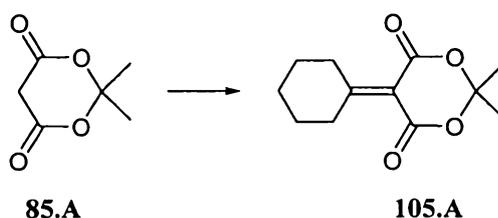
or

**104**

[01524] 3-Cyclopropyl-3-(3-(((2-((1S)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid or 3-cyclopropyl-3-(3-(((2-((1R)-2,2-dimethylcyclopentyl)-2'-fluoro-5'-(methoxy)-1,1'-biphenyl-4-yl)methyl)oxy)phenyl)butanoic acid (104). 104 was synthesized by a method analogous to that used to prepare compound 103. (MS ESI (neg.) m/e: 529.3 (M-H)).

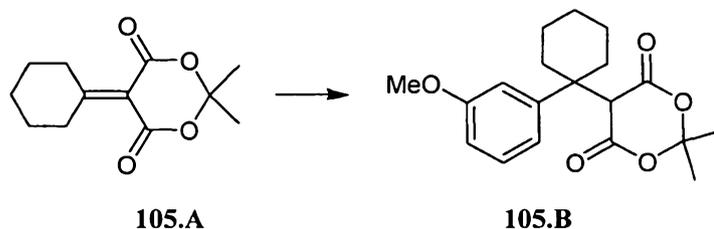
[01525] Example 105

[01526] Synthesis of methyl 2-(1-(3-hydroxyphenyl)cyclohexyl)acetate (105).

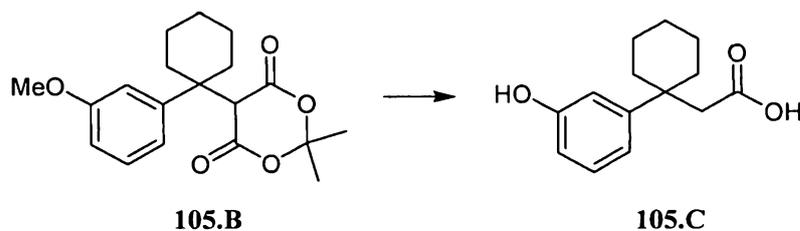
**85.A****105.A**

[01527] 5-Cyclohexylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (105.A). A titanium tetrachloride solution (36.0 mL, 36.0 mmol) (1M solution in DCM) was added slowly to a cooled (0°C) round bottom flask containing dry THF (75 mL). To the resulting yellow slurry was slowly added the 2,2-dimethyl-1,3-dioxane-4,6-dione (2.50 g, 17.0 mmol)(commercially available from Aldrich) and cyclohexanone (1.80 mL, 17.0 mmol)(commercially available from Aldrich) dissolved in THF (25 mL). Pyridine(7.0 mL, 87.0 mmol) was then added and the resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction was then quenched with water (200 mL) and the mixture was extracted with ether (2 x 300 mL). The combined organic layers

were washed with saturated sodium bicarbonate solution (2 x 150 mL) and brine (1 x 100 mL) and dried over magnesium sulfate. The filtrate was concentrated, and the residue was recrystallized using ether and hexanes to give 5-cyclohexylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (1.86 g, 48% yield). MS ESI (neg.) m/e: 223.1 (M-H)⁻.

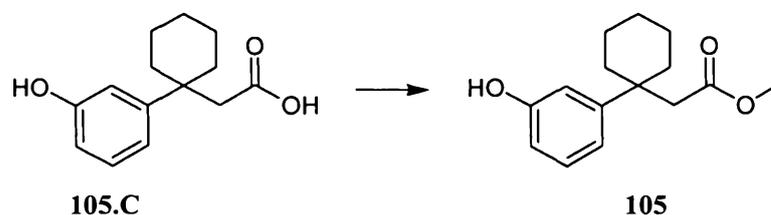


[01528] **5-(1-(3-Methoxyphenyl)cyclohexyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (105.B)**. 5-(2-(3-Methoxyphenyl)propan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**105.B**) was prepared from **105.A** and (3-methoxyphenyl)magnesium bromide (1.0 M in THF solution from Aldrich) using a procedure described in Huang, X.; et. al.; Tetrahedron Letters; 1982, (1); pp. 75-76. MS ESI (neg.) m/e: 331.1 (M-H)⁻.



[01529] **2-(1-(3-Hydroxyphenyl)cyclohexyl)acetic acid (105.C)**. 5-(1-(3-Methoxyphenyl)cyclohexyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**105.B**) (985 mg, 2.96 mmol) was dissolved in N-methylpyrrolidinone (6.0 mL) and water (53.4 μ L, 2.96 mmol) was added. The solution was heated at 120°C for three hours and LCMS indicated conversion to the anisole carboxylic acid intermediate. The reaction was cooled and NaOH (530 mg, 13.3 mmol) and commercially available dodecane-1-thiol (2.47 mL, 10.4 mmol) were added and the mixture was reheated to 120°C and stirred for 2.5 days. The reaction was cooled and then diluted with water (75 mL). The mixture was extracted with ether (2 x 75 mL). The aqueous layer was then acidified with hydrochloric acid and extracted with EtOAc (3 x 75 mL). The combined EtOAc layers were washed with water (2 x 100 mL) and brine (1 x 75 mL) and dried over magnesium sulfate. The filtrate was concentrated to give 2-(1-(3-hydroxyphenyl)cyclohexyl)acetic acid **105.C** (1.01 g, 145%

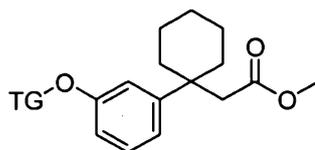
yield) with acceptable purity (contains residual N-methylpyrrolidone) to take to the next reaction. MS ESI (neg.) m/e: 233.1 (M-H)⁻.

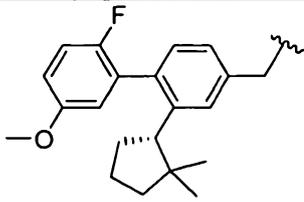
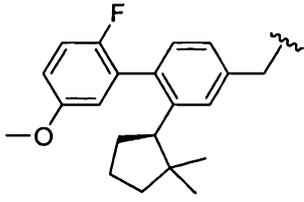
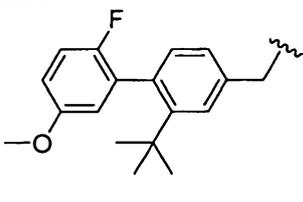


[01530] **Methyl 2-(1-(3-hydroxyphenyl)cyclohexyl)acetate (105).** The crude 2-(1-(3-hydroxyphenyl)cyclohexyl)acetic acid **105.C** (1.01 g) was dissolved in MeOH (15 mL) and a catalytic (~10 drops) amount of concentrated sulfuric acid was added. The mixture was then refluxed for 16 hours and then cooled to room temperature. The reaction was then made basic with saturated sodium bicarbonate solution and concentrated to dryness. The residue was then dissolved in EtOAc and water and the layers were separated. The aqueous layer was extracted (2 x 75 mL) with EtOAc. The combined organic layers were then washed with brine (1 x 75 mL) and dried over magnesium sulfate. The crude product was purified by medium pressure chromatography (silica, 0 to 15% EtOAc : DCM) to give methyl 2-(1-(3-hydroxyphenyl)cyclohexyl)acetate **105** (560 mg, 52% yield). MS ESI (pos.) m/e: 266.2 (M+H₂O)⁺.

[01531] The following compounds were prepared from methyl 2-(1-(3-hydroxyphenyl)cyclohexyl)acetate (**105**) and the appropriate halomethyl or hydroxymethyl compound according to the methods described herein.

Table 31



Compound	TG	Compound	TG
105.1	 <p>or</p> 	105.2	

[01532] (1-{3-[2-((S)-2,2-Dimethyl-cyclopentyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-phenyl}-cyclohexyl)-acetic acid or (1-{3-[2-((R)-2,2-dimethyl-cyclopentyl)-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-phenyl}-cyclohexyl)-acetic acid (105.1). MS ESI (neg.) m/e: 543.2 (M-H)⁻.

[01533] (1-{3-[2-tert-Butyl-2'-fluoro-5'-methoxy-biphenyl-4-ylmethoxy]-phenyl}-cyclohexyl)-acetic acid (105.2). MS ESI (neg.) m/e: 503.2 (M-H)⁻.

[01534] **Biological Activity**

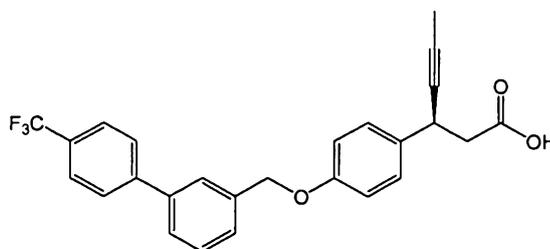
[01535] The GPR40 agonist compounds described herein possess unique, surprising, and highly advantageous properties that are distinct from previously described GPR40 agonists. Unexpectedly, compounds of the present invention have been found to bind to a different site compared to other GPR40 agonists and in general have greater activity than previously described GPR40 agonists in functional assays. For example, compounds of the present invention were found to possess activity on the GPR40 receptor that was similar to the fatty acid natural ligands, indicating that they were full agonists. These results indicate that previously described GPR40 agonists and those of the present invention are pharmacologically distinct.

[01536] Competition binding assays were performed on A9 membranes expressing GPR40. The membranes were incubated with different concentrations of Comparative Compound 1, Example 14, or Example 9 in the presence of 5 nM [³H] labeled Comparative Compound 1 for 4 hours at room temperature. [³H] labeled

Comparative Compound 1 was displaced completely by the unlabeled Comparative Compound 1 exhibiting homologous competition such that the unlabeled Comparative Compound 1 competes for the same site on the receptor as does the [³H] labeled compound. However, surprisingly and unexpectedly, Example 14 and Example 9 did not displace the bound [³H] labeled Comparative Compound 1. Rather, even more surprisingly, addition of Example 9 or Example 14 enhanced the binding of the radioligand (Comparative Compound 1) to the receptor. The non-competitive behavior displayed shows positive allosterism of these compounds in the presence of Comparative Compound 1. The positive cooperativity of these compounds is greater than 1 when the receptor is bound to Comparative Compound 1. Thus, competition binding assays show that the compounds of the present invention agonists bind to a distinct site on the GPR40 receptor compared to other GPR40 agonists.

[01537] In GPR40 cell signaling assays, the compounds of the present invention displayed surprisingly enhanced activity compared with previously described GPR40 agonists. In aequorin assays, using a cell line stably expressing GPR40, the E_{max} of the compounds of the present invention was greater than that of previously described GPR40 agonists and similar to that of the GPR40 natural ligands, fatty acids (Figure 2). Thus, the compounds of the present invention appear to be full agonists while the previously described GPR40 compounds were partial agonists. Briefly, the Aequorin assays were performed on doubly stable CHO cells expressing GPR40 and Aequorin DNA. Ligand-induced calcium mobilization was observed as indicated by an increase in the Aequorin luminescence which is in proportion to the calcium released upon activation of the receptor. The luminescence was recorded over a period of 20 seconds with a Microlumet luminometer (Berthold). Example 14 and Example 66.4 were found to be potent full agonists as compared with endogenous full agonists α -linolenic acid and docosahexaenoic acid. The efficacy of the compound of the present invention was surprisingly and unexpectedly improved over Comparative Compound 1. The enhanced activity of the compounds of the present invention compared to previously described GPR40 agonists was also demonstrated in inositol phosphate accumulation assays (Figure 3). The inositol phosphate assay was performed on an A9 cell line stably transfected with GPR40 (A9_GPR40). The cells were incubated with different concentrations of compounds and [³H] inositol accumulation was measured after 1 hour. Example 14 and Example 9 compounds were found to activate the GPR40 receptor as potent full agonists as compared with Comparative Compound 1 which acted as a partial agonist.

[01538] The enhanced activity of the compounds of the present invention was also observed in primary cell culture experiments. Islets were isolated from rodents and insulin secretion in response to the compounds of the present invention and certain previously described GPR40 agonists was measured. More specifically, islets were isolated from the pancreas of mice using collagenase digestion followed by purification on a histopaque gradient. Islets were hand-picked and then incubated for one hour in KRBH medium containing 16.7 mM dextrose, 0.1% human serum albumin, and test compounds diluted to a specified concentration. Insulin secreted into the culture supernatant was measured using an insulin ELISA. Dose response plots were graphed using Graphpad Prism software. The compounds of the present invention secreted unexpectedly greater levels of insulin compared with the previously described GPR40 agonists (Figure 4) tested. The enhanced activity of the compounds of the present invention indicates that these compounds are more effective than previously described GPR40 agonists in treating type 2 diabetes, metabolic syndrome, and other conditions where enhanced GPR40 activity may result in therapeutic utility. With respect to Figures 1-4, the structure of Comparative Compound 1 is shown below.



Comparative Compound 1

The synthesis of Comparative Compound 1 is set forth in Example 2 of US Patent Publication No. US2006/0004012 which is hereby incorporated herein by reference.

Cell-based Aequorin Assay

[01539] Cell-based aequorin assays were employed to characterize the modulatory activity of compounds on the GPR40 signaling pathway. In an exemplary assay, CHO cells were stably transfected with both GPR40 and Aequorin (Euroscreen). Cells were detached from the tissue culture dish with 2 mL of trypsin (0.25%(w/v)). Trypsinization was halted with 28 mL of Hanks Buffered Salt Solution containing 20 mM HEPES (H/HBSS) and 0.01% fatty acid-free human serum albumin (HSA). Coelantrazine is added to 1 $\mu\text{g}/\text{mL}$, and the cells were incubated for 2 hours at room temperature. Compounds were dissolved in DMSO for preparation of 10 mM stock solutions.

Compounds were diluted in H/HBSS containing 0.01% HSA. Serial dilutions of the test compounds were prepared to determine dose response.

[01540] Aequorin luminescence measurements were made using an EG&G Berthold 96-well luminometer, and the response was measured over a 20 second interval after cells and compounds were mixed. The maximum relative light units was plotted to determine dose response. The EC₅₀ (effective concentration to reach 50% maximal response) was determined from the dose response plot.

[01541] Table 32 presents representative data (EC₅₀ values) obtained for exemplary compounds of the invention for the activation of human GPR40.

Inositol Phosphate Accumulation Assay

[01542] An A9 cell line stably transfected with GPR40 (A9_GPR40) was used in IP accumulation assays. A9_GPR40 cells were plated in 96-well plates containing 20,000 cells/well in DMEM containing 10% FBS. After the cells attached to the well surface, the media was replaced with inositol free DMEM containing 10% dialyzed FBS and 1 μCi, mL ³H-inositol and incubated for 16 hours. Compounds were diluted in HBSS/10 mM LiCl containing a desired amount of HSA and added directly to cells. Following 1 hour incubation at 37°C, the media was replaced with 100 μL of 20 mM formic acid to quench the reaction. 50 μL of the extract was then added to 100 μL of SPA beads, incubated overnight, and measured on a TopCount the following day.

[01543] The stereoisomers in Table 32 are as specified, i.e., S-enantiomers or R-enantiomers, and if not specified, or if shown with wavy bonds, are mixtures of S-enantiomers and R-enantiomers. In addition, the present invention provides the S-enantiomers, the R-enantiomers, and mixtures of both S-enantiomers and R-enantiomers including racemates of each compound prepared according to the synthetic methods described herein or adapted with the necessary minor modifications from these methods.

Insulin Secretion Assay

[01544] Human islets were isolated from cadaveric donors. Islets were treated with trypsin (0.25%(w/v) and cells were seeded in 96-well plates containing 3,000 cells per well. Cells were cultured in Roswell Park Memorial Institute (RMPI) media containing 10% fetal bovine serum.

[01545] For determination of insulin secretion, media was removed from islet cells and replaced with Krebs-Ringer bicarbonate buffer containing 10 mM HEPES

(KRBH) and 2 mM glucose. After one hour incubation, media was replaced with KRBH containing 11.2 mM glucose and test compounds. Insulin released into the medium from the islet cells was measured using a scintillation proximity assay (SPA).

[01546] For determination of insulin secretion from rodent islets, C57/Bl6 mice were euthanized with carbon dioxide gas. The pancreatic bile duct was clamped proximal to the duodenum and then cannulated. H/HBSS containing 0.75 mg/mL collagenase XI (Sigma) was then infused into the pancreas through the cannula. The pancreas was excised and then incubated at 37°C for 13 minutes to complete enzymatic digestion. The collagenase digestion was quenched in H/HBSS containing 1% BSA and washed once in the same buffer. Islets can be purified using density gradient centrifugation using Histopaque (Sigma) and were hand-picked under a stereomicroscope.

[01547] Islets were cultured overnight in Roswell Park Memorial Institute (RMPI) media containing 10% fetal bovine serum and 50 uM beta-mercaptoethanol. Following overnight culture, islets were incubated in KRBH containing 2.8 mM glucose for one hour.

[01548] For determination of insulin secretion, islets were incubated in DMEM containing 12.5 mM glucose and test compounds for one hour. Insulin released into the culture medium from the islets was measured using an insulin ELISA.

GLP-1 Secretion Experiments

In Vitro GLP-1 Secretion in Primary Cell Cultures

[01549] Pregnant Wistar rats were obtained from Harlan (Indianapolis). Fetal rat intestinal cells (FRIC) were isolated from E19 rat embryos following a protocol published by Brubaker and Vranic, *Endocrinology* 120(5):1976-85, 1987 which is hereby incorporated by reference in its entirety and for all purposes as if specifically set forth herein. Briefly, female Wistar rats were euthanized at day 19 of pregnancy and fetuses were excised. The small intestine was harvested from each fetus, minced, and washed with modified Hank's Buffered Salt Solution (HBSS) (Sigma-Aldrich). Cells were dispersed by two sequential 20 minute rounds of digestion in collagenase buffer (0.5 mg/mL type H SigmaBlend collagenase, 0.5mg/mL hyaluronidase, 0.05mg/mL DNase I) at 37°C. Dispersed cells were washed twice with HBSS, and cultured in poly-D-lysine coated 96-well plates in Clonetics BEGM epithelial growth medium. After 24 hours, cells were incubated for 2 hours with dilutions of small molecule GPR40 modulators prepared from a 10 mM DMSO stock solution in HBSS. Secreted active GLP-1 (7-36 amide) and GLP-1 (7-37) was measured in culture media using an ELISA kit (Linco

Research, St. Charles, MI). The experiments demonstrate that the example compounds significantly increase GLP-1 secretion.

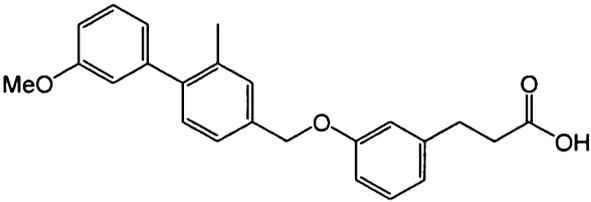
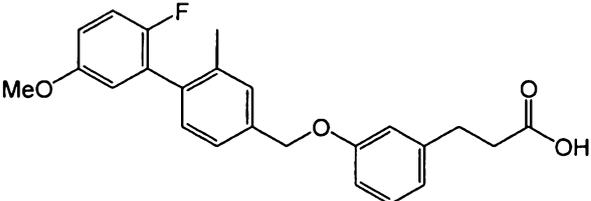
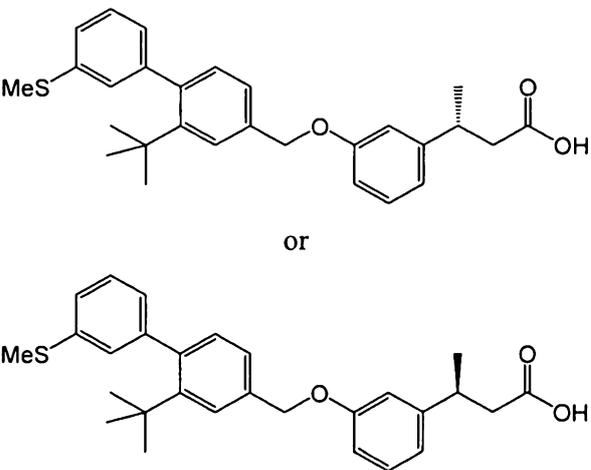
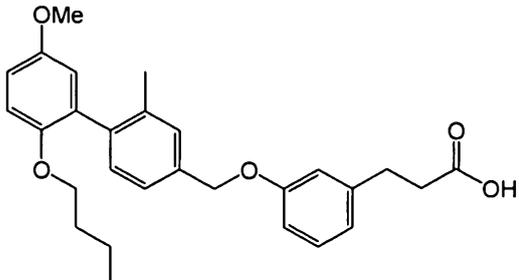
In Vivo GLP-1 Secretion in C57Bl6 Mice

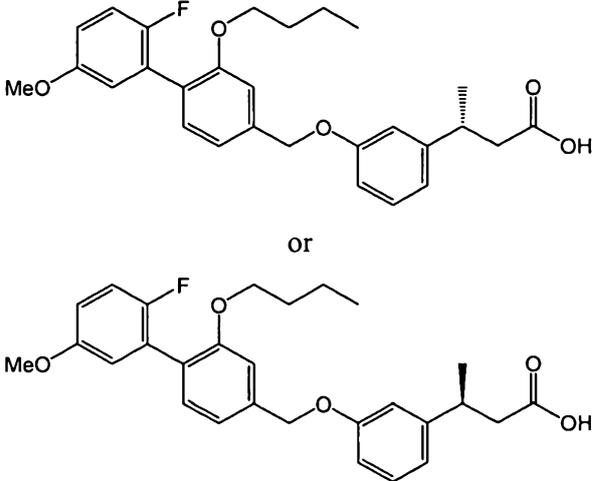
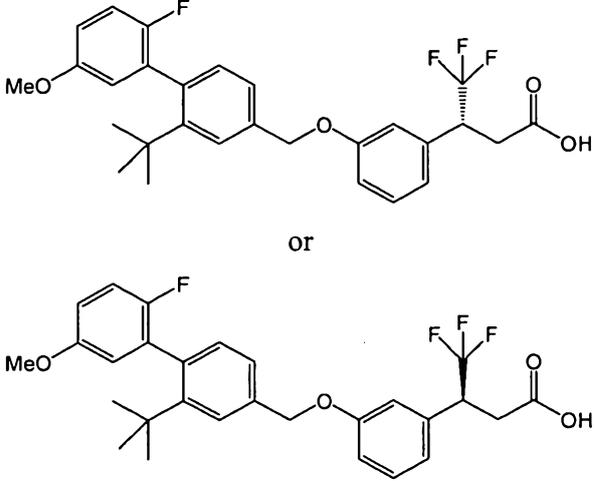
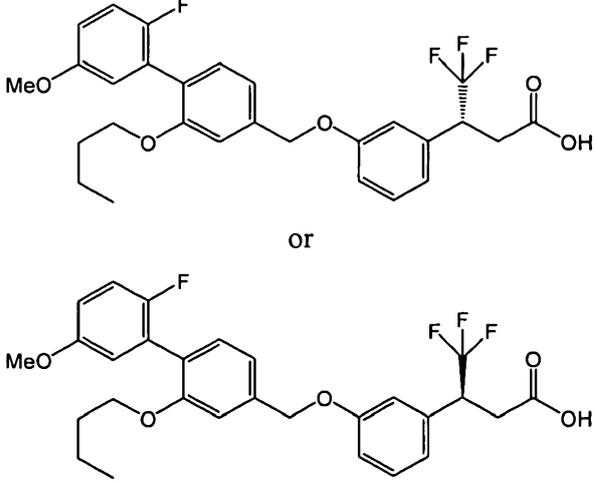
[01550] Male, 12 week old, C57Bl6 mice were obtained from The Jackson Laboratory (Bar Harbor, Maine). All mice were group-housed in a humidity and temperature-controlled room with a 12 hour light/dark cycle and ad libitum access to chow (Teklad 2018S) and water. The animals were assigned into vehicle or treatment groups. The experiments were conducted under overnight fasted or non-fasted conditions. Blood samples were taken at 0, 15, 30, 60 and 120 minutes after the dose. Plasma active form GLP-1 concentrations were measured using GLP-1 ELISA kits (Linco Research, St. Charles, MI). These experiments demonstrate that the example compounds significantly increased plasma levels of GLP-1 in normal mice after administration in both the fasted and non-fasted states.

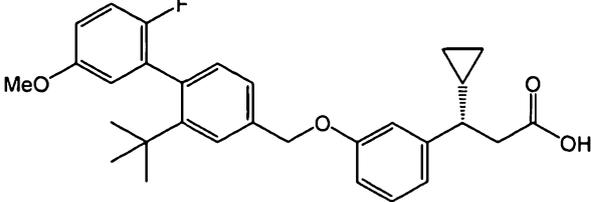
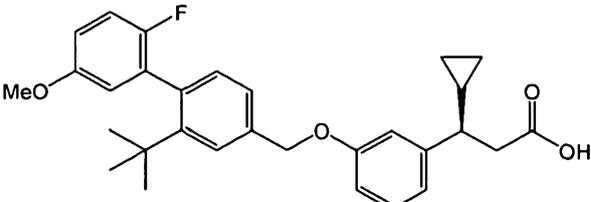
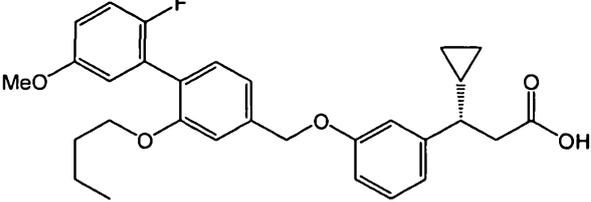
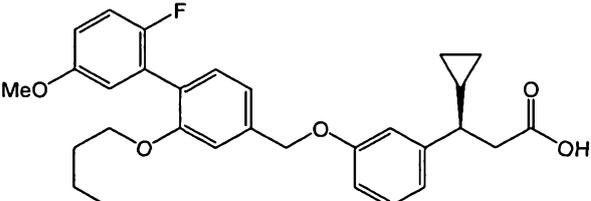
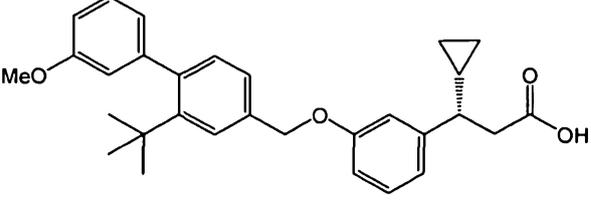
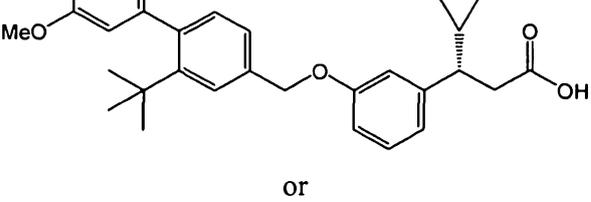
In Vivo GLP-1 Secretion in Diabetic Mice

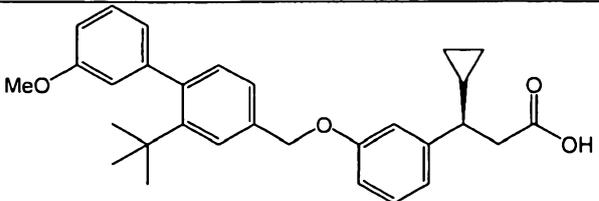
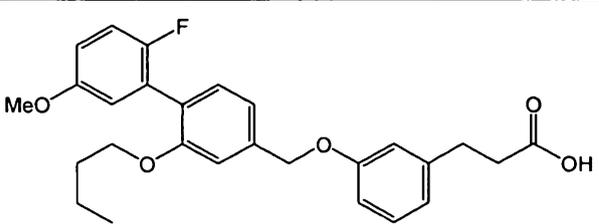
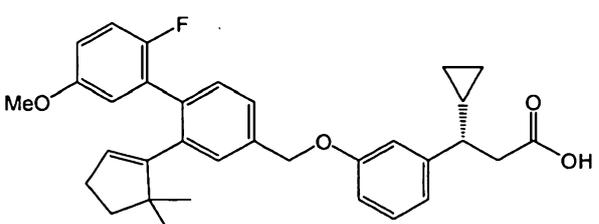
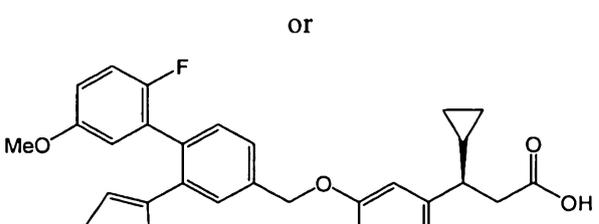
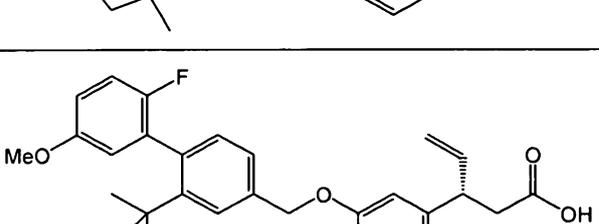
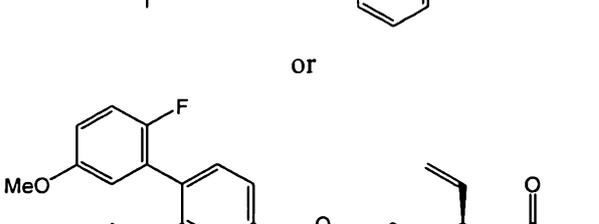
[01551] Male, 4 week old, C57Bl6 mice were obtained from The Jackson Laboratory (Bar Harbor, Maine). All mice were group-housed in a humidity and temperature-controlled room with a 12 hour light/dark cycle and ad libitum access to a 35% w/w fat-enriched diet (Bioserv) and water. The diabetic condition was established by 4 weeks of fat-enriched diet feeding and a dose of streptozotocin (Sigma Aldrich) at 95 mg/kg i.p. injection. The animals were assigned into vehicle or treatment groups. The experiments were conducted under non-fasted conditions. Blood samples were taken at 0, 15, 30, 60, 120 and 240 minutes after the dose. Plasma active form GLP-1 concentrations were measured using GLP-1 ELISA kits (Linco Research, St. Charles, MI). These experiments demonstrate that the example compounds significantly increased plasma levels of GLP-1 in diabetic mice after administration in the non-fasted state.

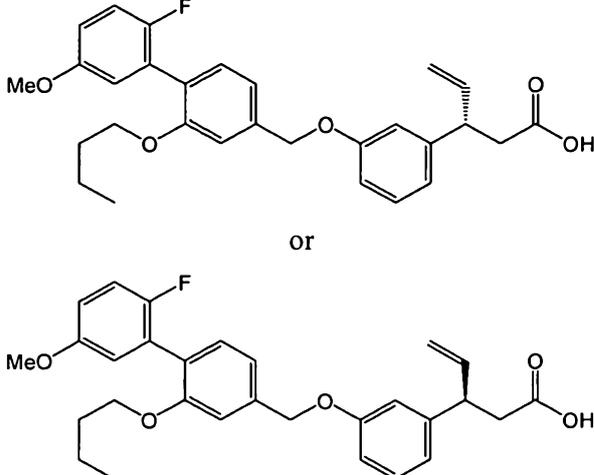
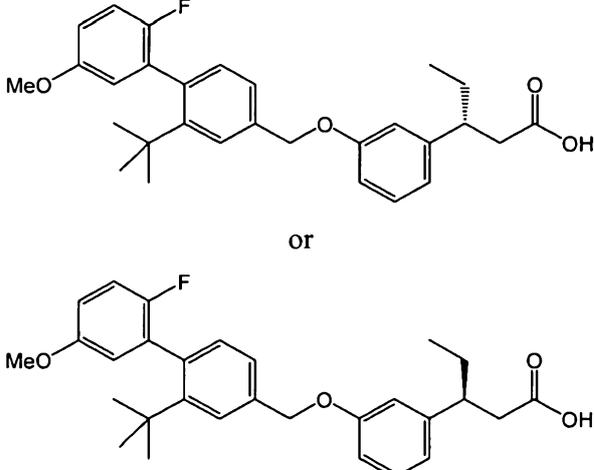
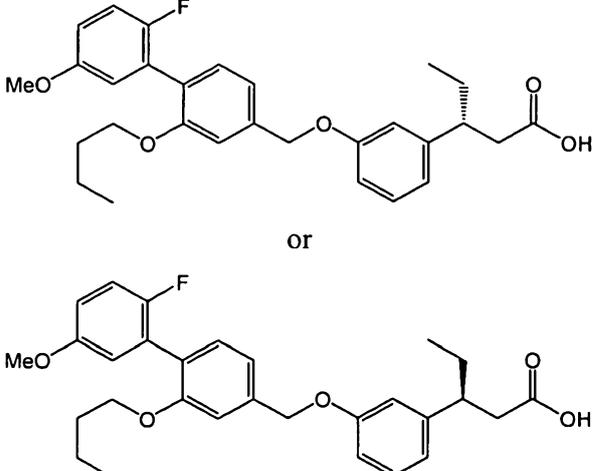
[01552] All publications and patent applications cited in this specification are hereby incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Each publication and patent application cited herein is incorporated in its entirety as if fully set forth herein. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

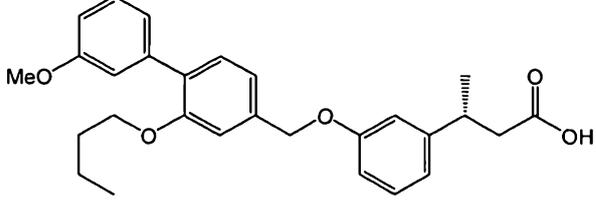
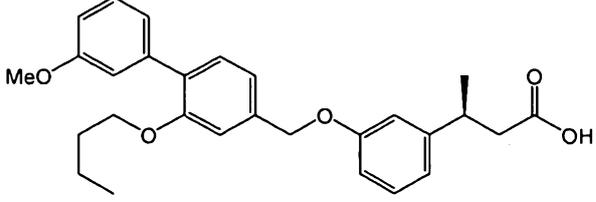
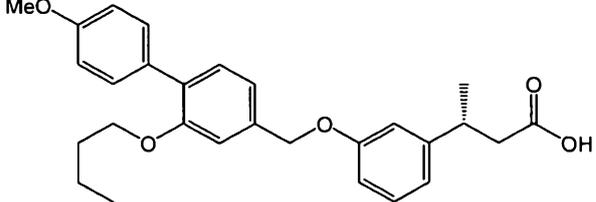
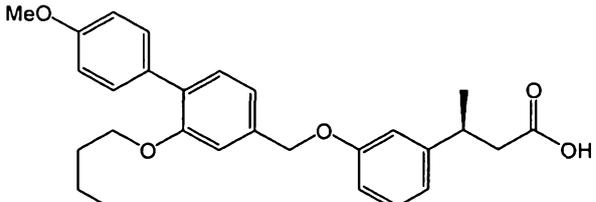
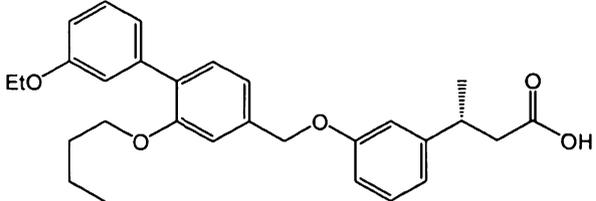
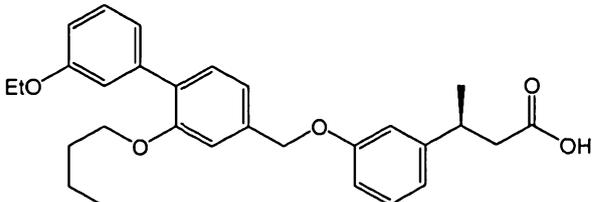
TABLE 32 Assay Data For Human GPR40			
No.	Structure ^a	AequorinEC ₅₀ ^{b,c}	IP3 EC ₅₀ ^{c,d}
1		++	ND ^e
2		+++	ND
3	 or	++	ND
4		++	ND

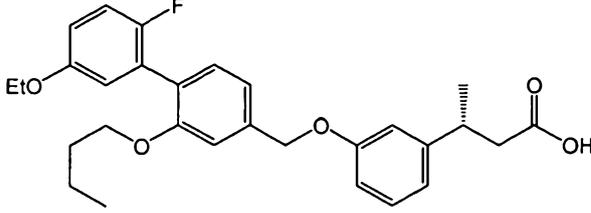
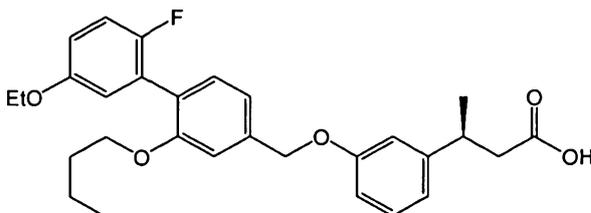
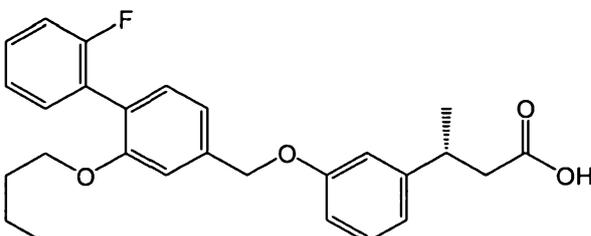
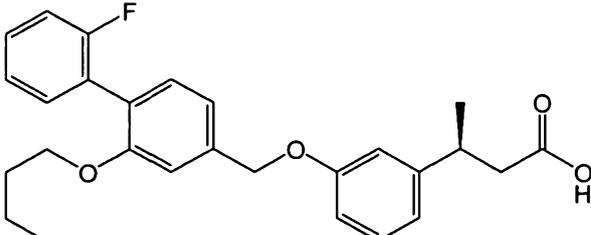
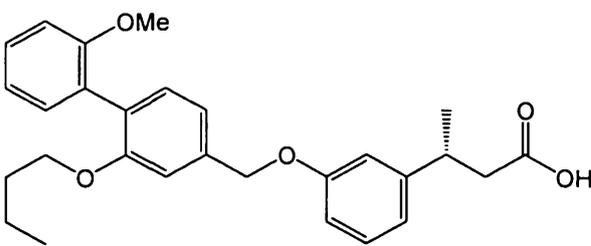
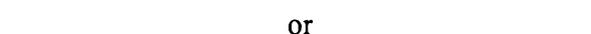
<p>5</p>	 <p>or</p>	<p>+++</p>	<p>+++</p>
<p>6</p>	 <p>or</p>	<p>++</p>	<p>+ / ++</p>
<p>7</p>	 <p>or</p>	<p>++</p>	<p>++</p>

<p>8</p>	 <p>or</p> 	<p>+++</p>	<p>+++</p>
<p>9</p>	 <p>or</p> 	<p>+++</p>	<p>+++</p>
<p>10</p>	<p>Enantiomer of 8</p>	<p>++</p>	<p>ND</p>
<p>11</p>	<p>Enantiomer of 9</p>	<p>++</p>	<p>ND</p>
<p>12</p>	 <p>or</p> 	<p>+++</p>	<p>+++</p>

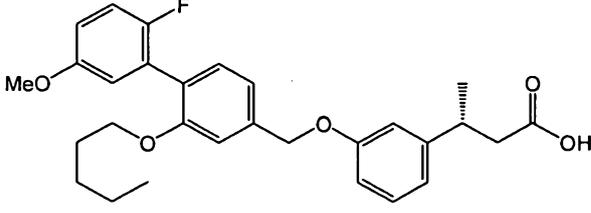
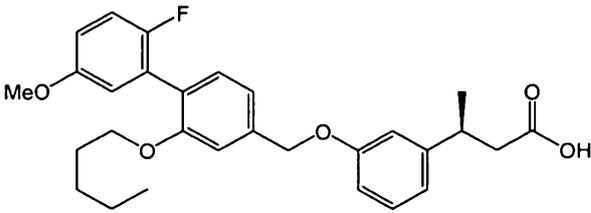
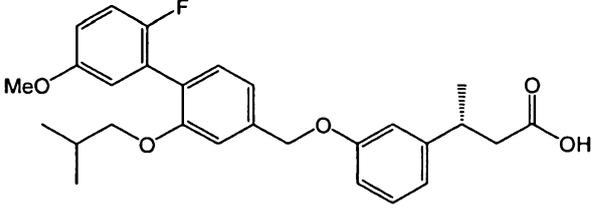
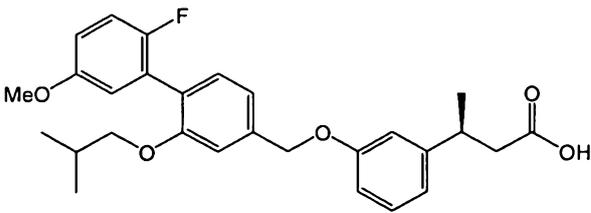
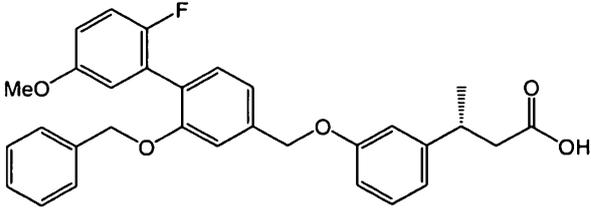
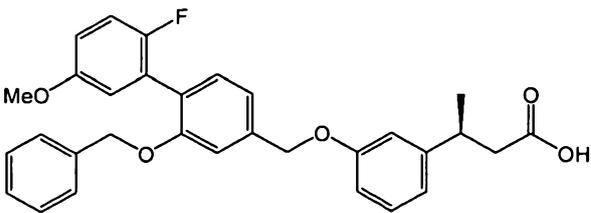
			
13		++	ND
14	 or 	+++	++++
15	 or 	++	ND

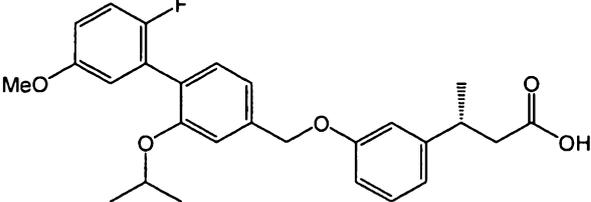
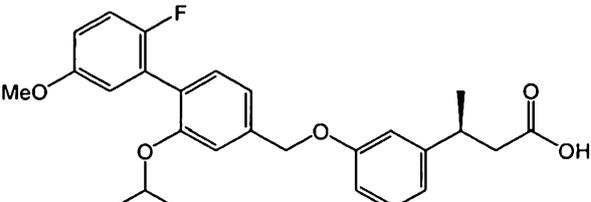
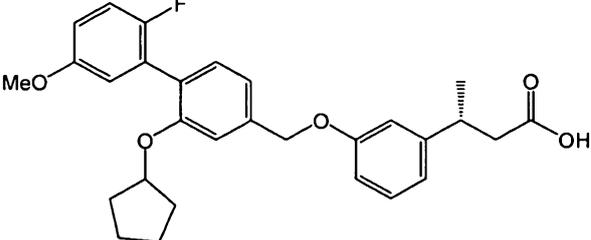
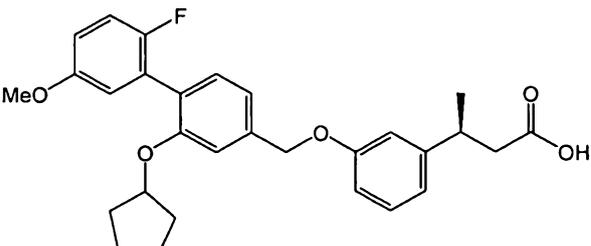
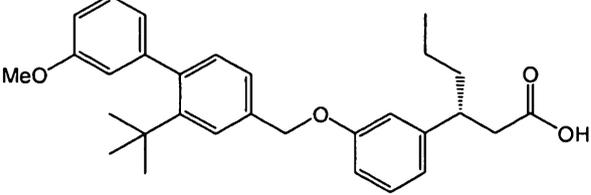
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<p>17</p>	 <p>or</p>	<p>+++</p>	<p>+++</p>
<p>18</p>	 <p>or</p>	<p>+++</p>	<p>+++</p>

19	Enantiomer of 15	++	ND
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21	 <p style="text-align: center;">or</p> 	++	ND
22	 <p style="text-align: center;">or</p> 	++	ND

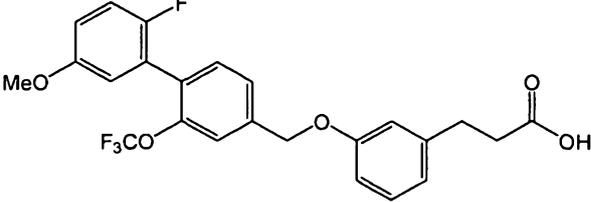
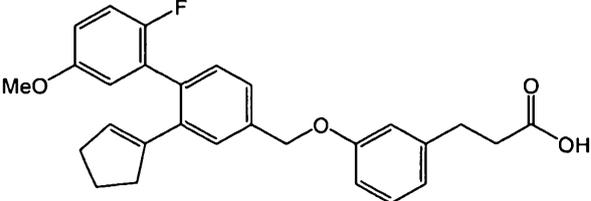
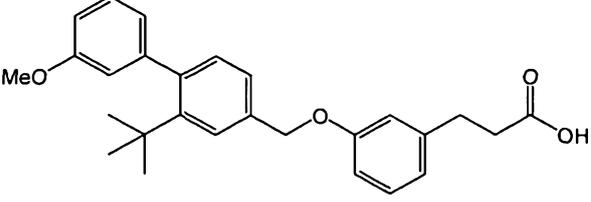
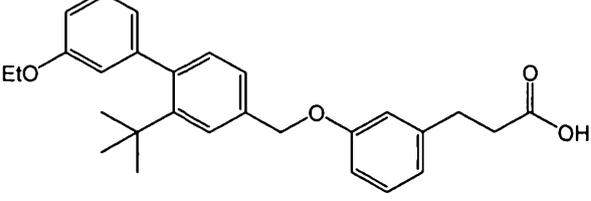
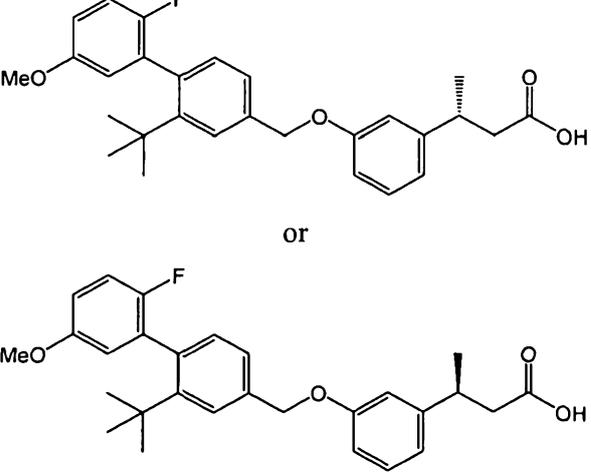
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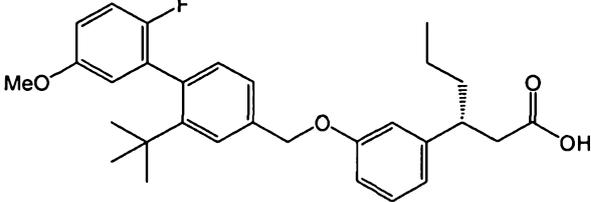
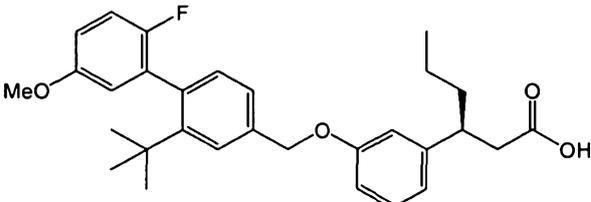
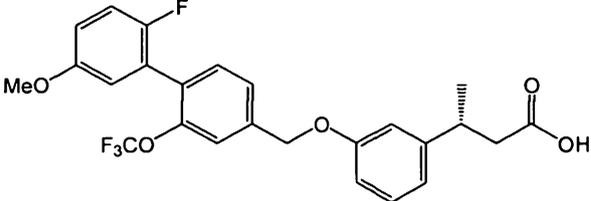
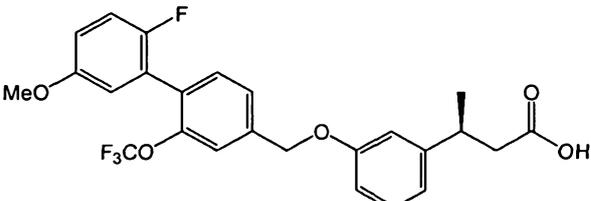
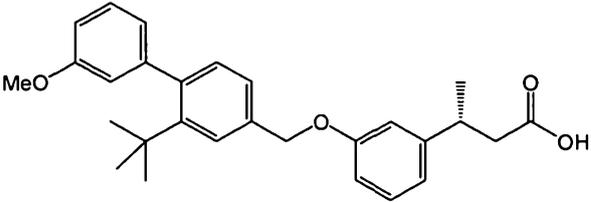
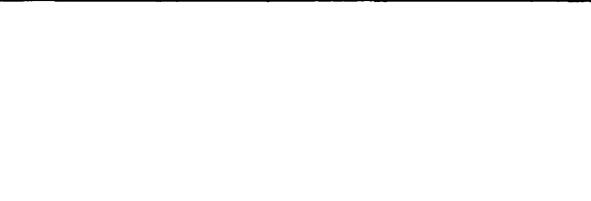
26	<p style="text-align: center;">or</p>	+++	ND
27	<p style="text-align: center;">or</p>	++	ND

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<p>29</p>	 <p>or</p> 	<p>+++</p>	<p>ND</p>
<p>30</p>	 <p>or</p> 	<p>++</p>	<p>ND</p>

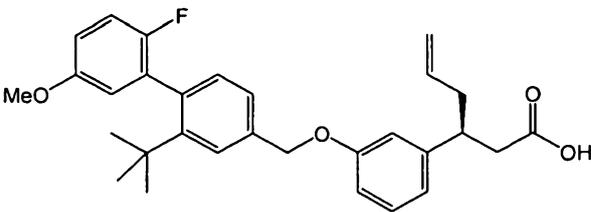
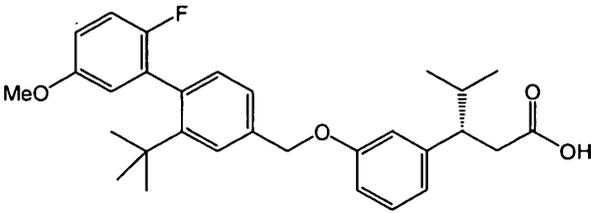
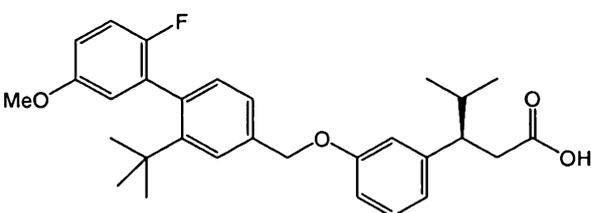
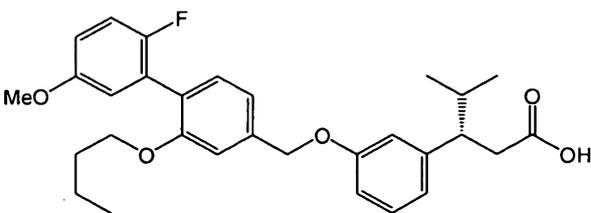
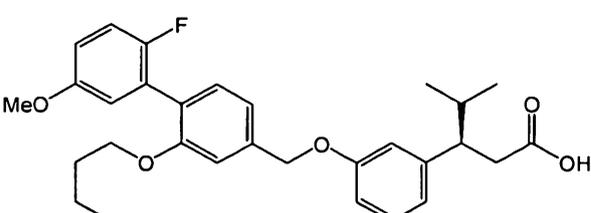
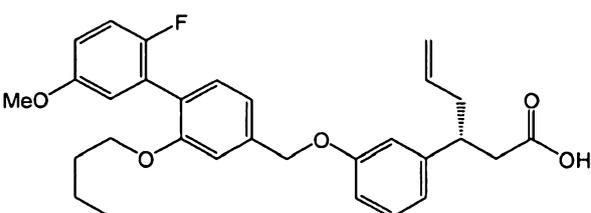
<p>31</p>	 <p style="text-align: center;">or</p> 	<p>+++</p>	<p>ND</p>
<p>32</p>	 <p style="text-align: center;">or</p> 	<p>+++</p>	<p>ND</p>
<p>33</p>	 <p style="text-align: center;">or</p> 	<p>+++</p>	<p>+++</p>

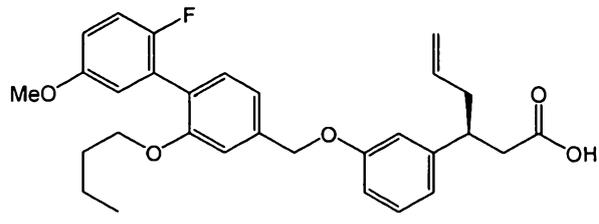
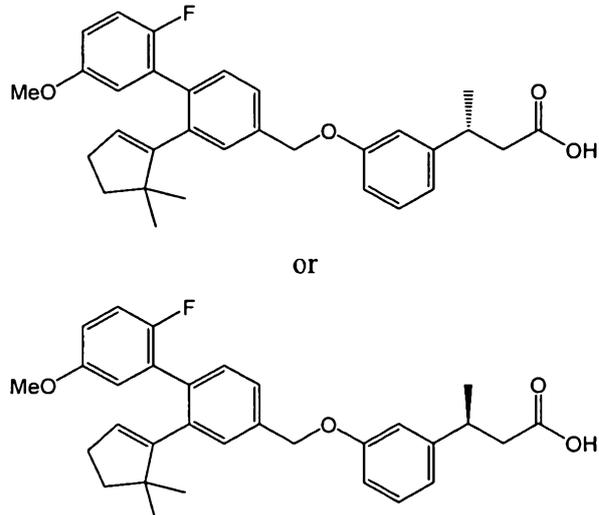
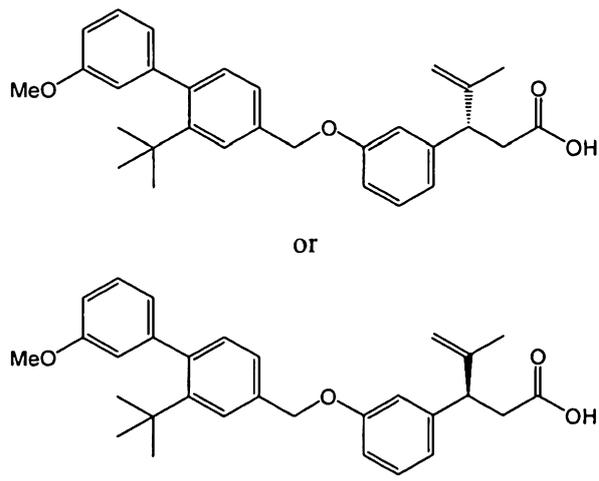
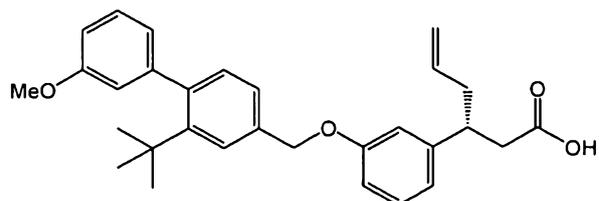
34		+++	+++
35	<p style="text-align: center;">or</p>	+++	+++
36		+++	+++
37		+++	+ / ++

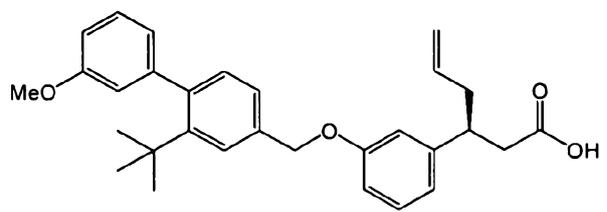
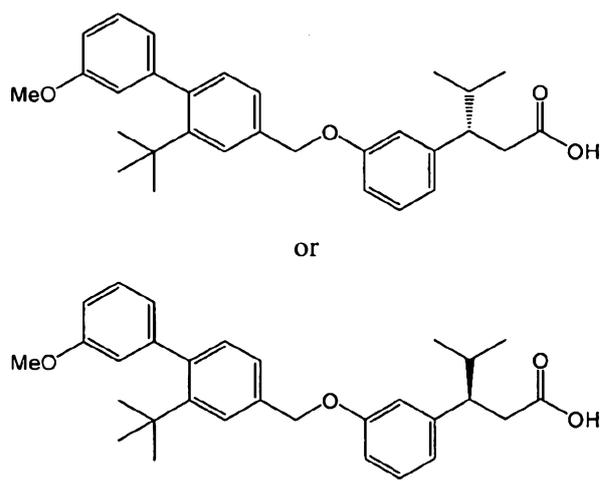
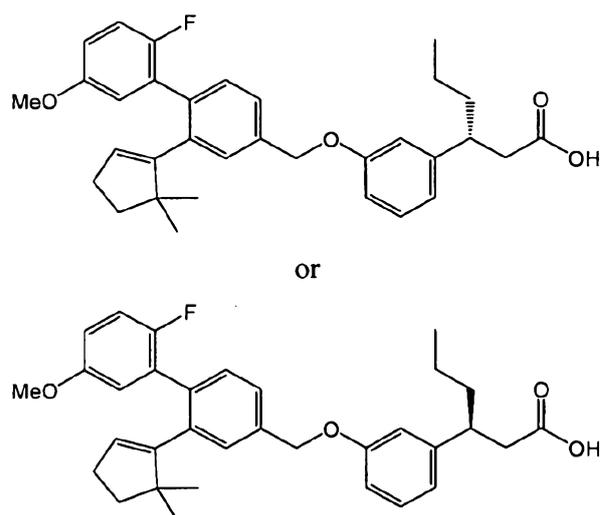
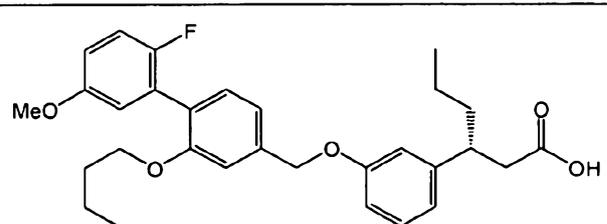
<p>38</p>		<p>+++</p>	<p>++</p>
<p>39</p>		<p>++</p>	<p>+++</p>
<p>40</p>		<p>+++</p>	<p>ND</p>
<p>41</p>		<p>++</p>	<p>ND</p>
<p>42</p>	<p>or</p> 	<p>+++</p>	<p>++</p>

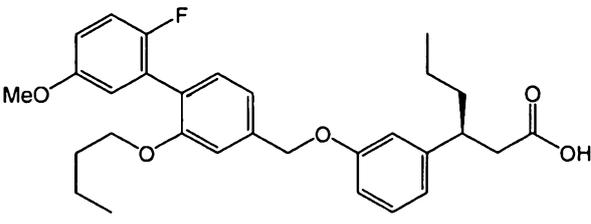
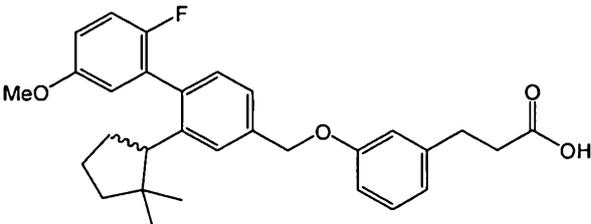
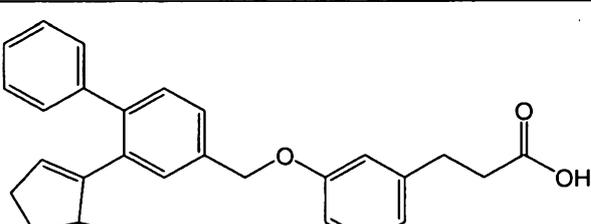
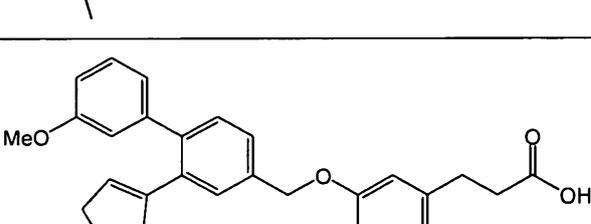
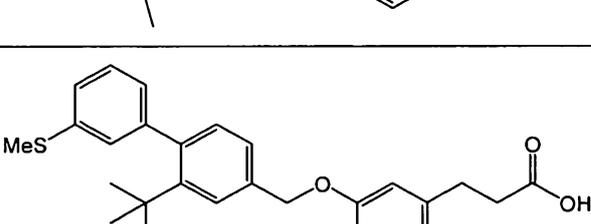
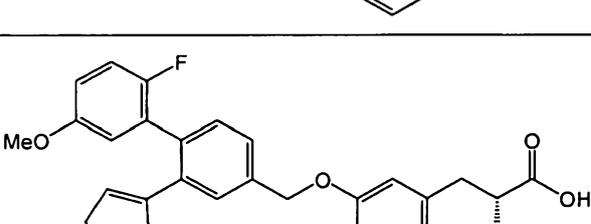
43	 <p style="text-align: center;">or</p> 	+++	+++
44	Enantiomer of 43	+++	+++
45	Enantiomer of 42	++	++
46	 <p style="text-align: center;">or</p> 	+++	++
47	 <p style="text-align: center;">or</p> 	+++	+++

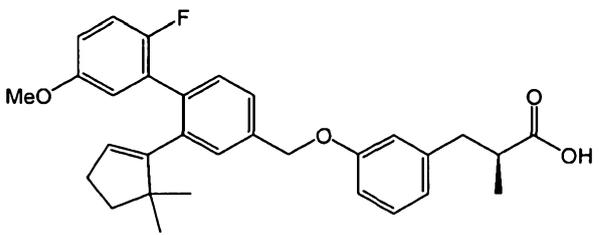
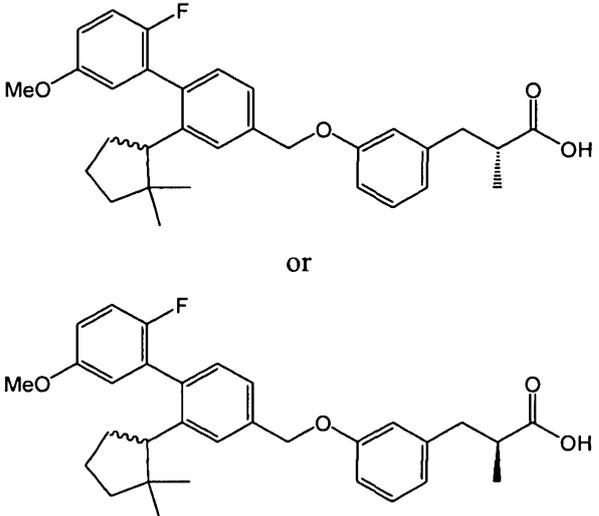
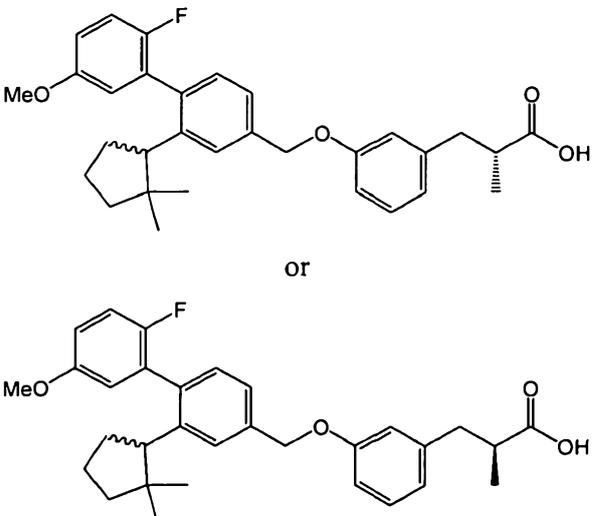
48	<p style="text-align: center;">or</p>	++	ND
49	Enantiomer of 48	+++	+++
50	<p style="text-align: center;">or</p>	++	++
51		+++	+++

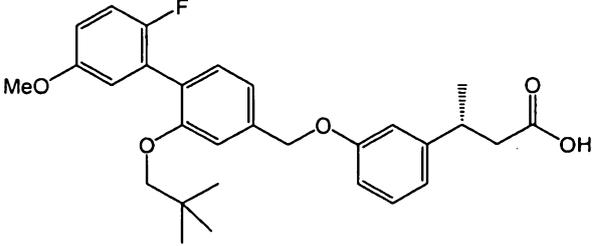
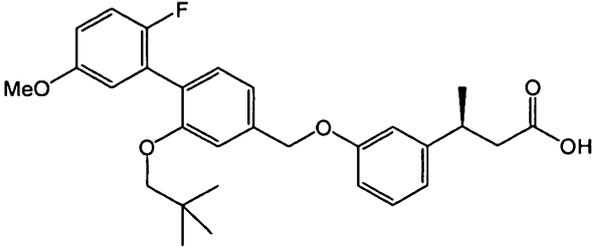
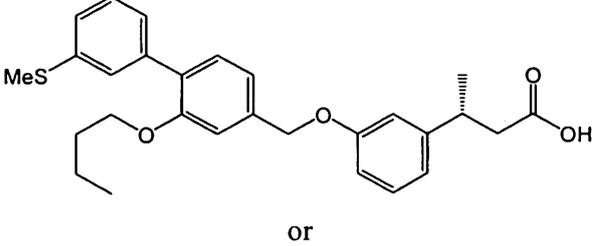
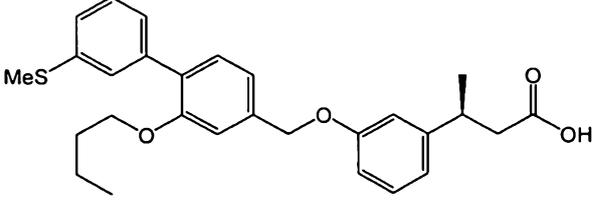
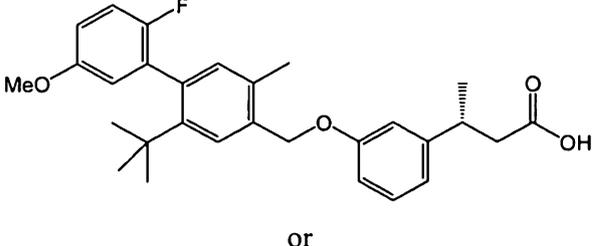
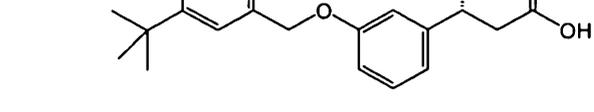
	<p>or</p> 		
52	 <p>or</p> 	++	ND
53	 <p>or</p> 	++	ND
54		++	ND

	<p>or</p> 		
55	<p>or</p> 	+++	++++
56	<p>or</p> 	+++	+++
57		+++	+++

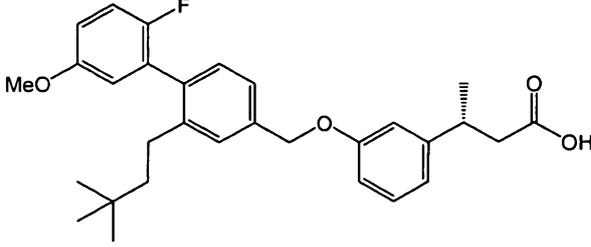
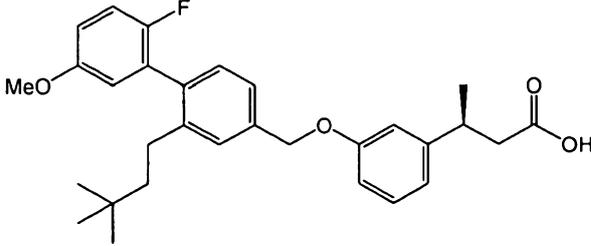
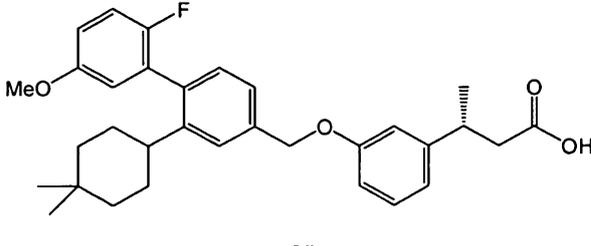
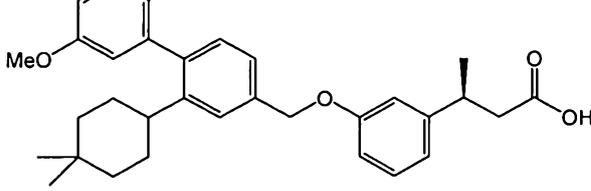
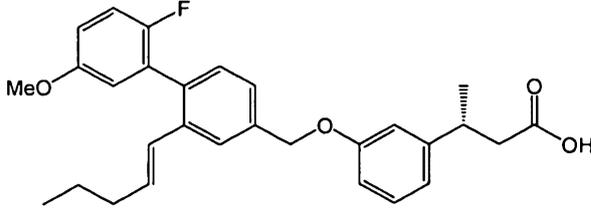
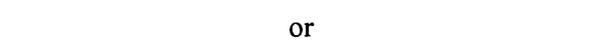
	<p>or</p> 		
58	<p>or</p> 	++	ND
59	<p>or</p> 	+++	++++
60		+++	+++

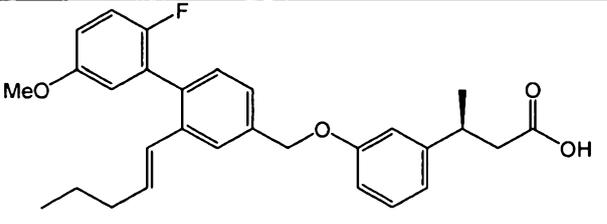
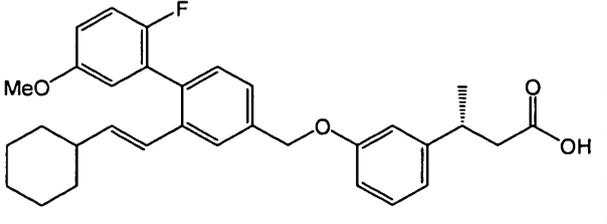
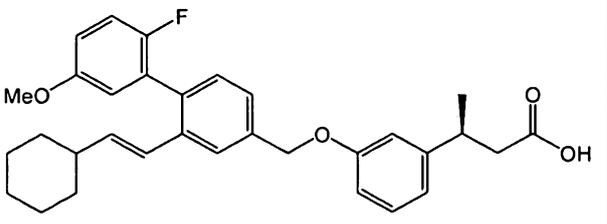
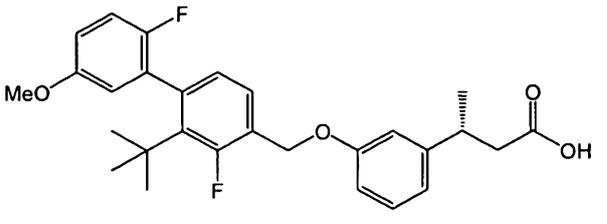
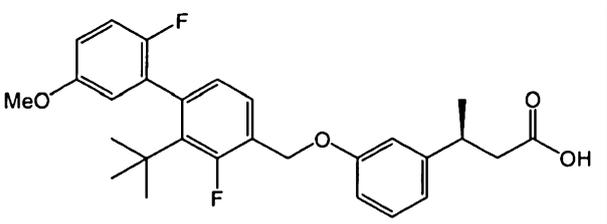
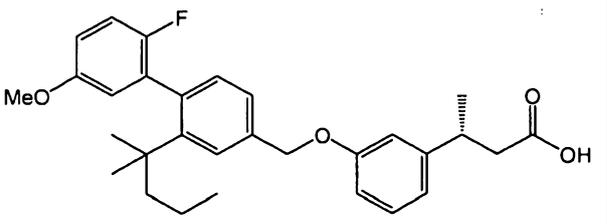
	or		
			
61.1		+++	ND
61.2		++	ND
61.3		+++	ND
61.4		++	ND
62.1		+++	ND

	<p>or</p> 		
62.2	<p>or</p> 	+++	ND
63.1	Enantiomer of 62.1	+++	ND
63.2	<p>or</p> 	+++	ND

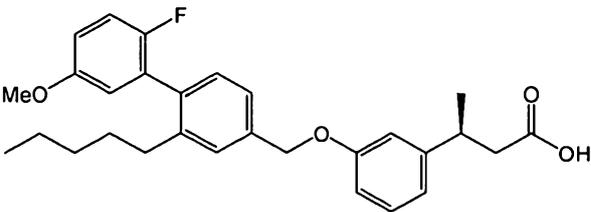
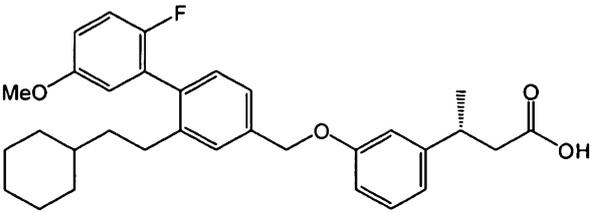
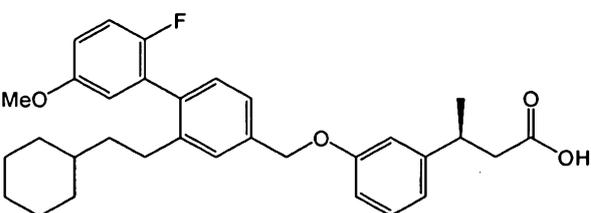
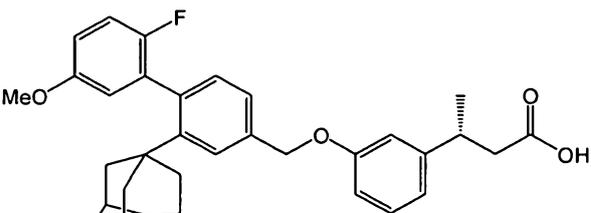
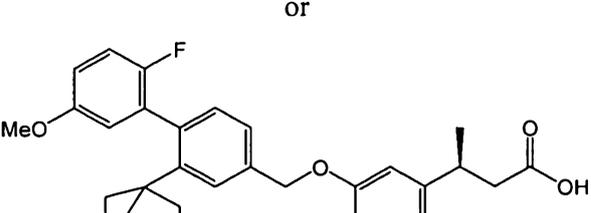
64.1	 <p>or</p> 	+++	ND
64.2	 <p>or</p> 	++	ND
64.3	 <p>or</p> 	++	ND

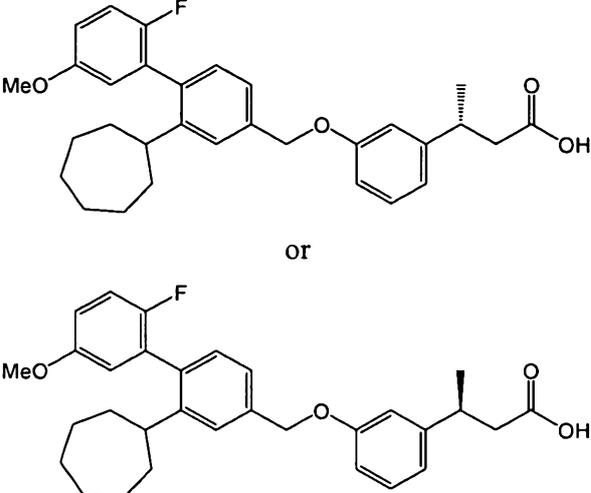
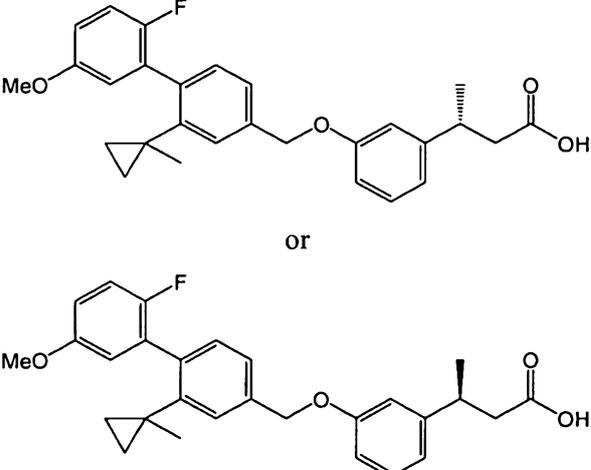
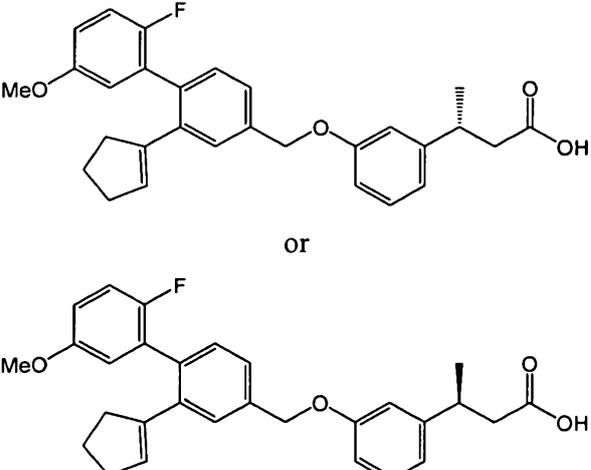
64.4	<p style="text-align: center;">or</p>	+++	++++
64.5	<p style="text-align: center;">or</p>	+++	++++

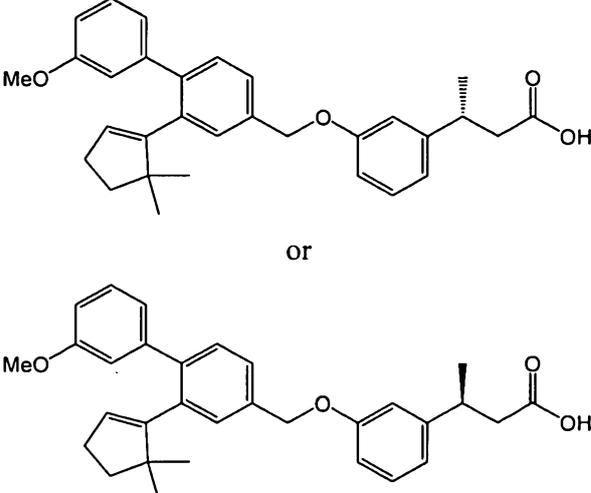
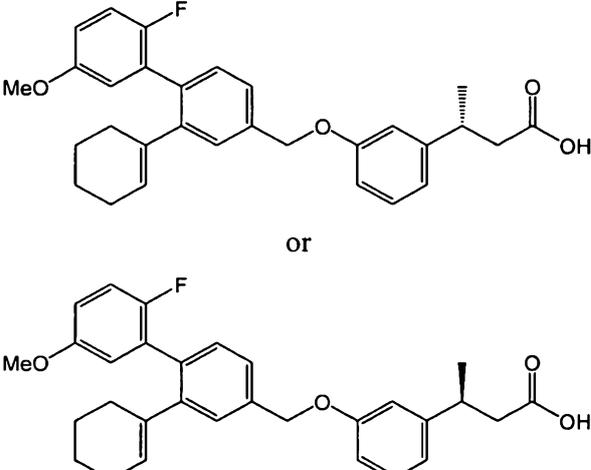
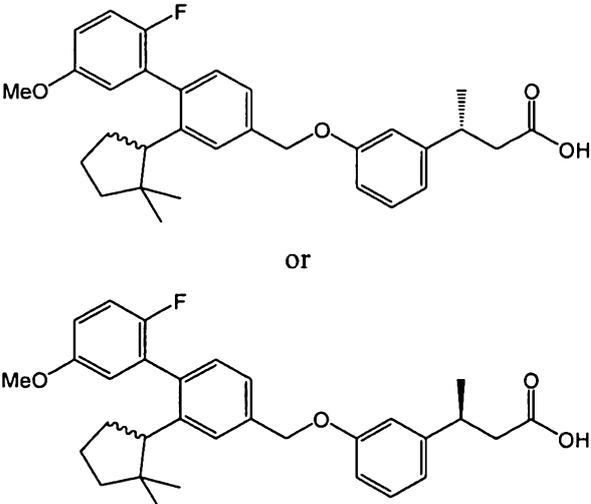
<p>64.6</p>	 <p>or</p> 	<p>+++</p>	<p>++++</p>
<p>64.7</p>	 <p>or</p> 	<p>+++</p>	<p>++++</p>
<p>64.8</p>	 <p>or</p> 	<p>+++</p>	<p>ND</p>

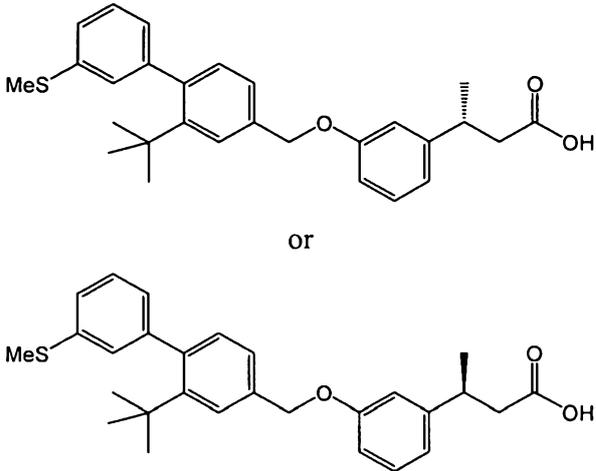
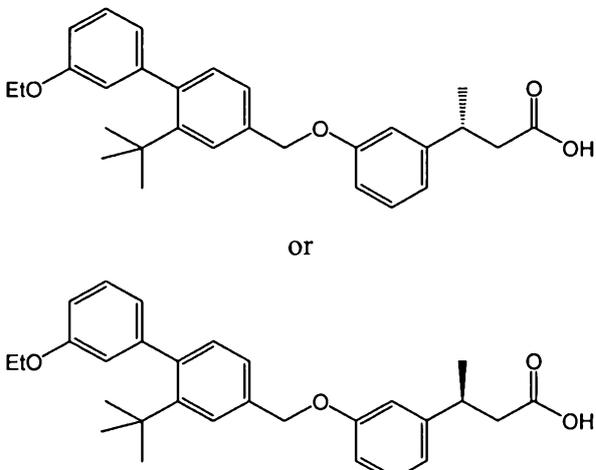
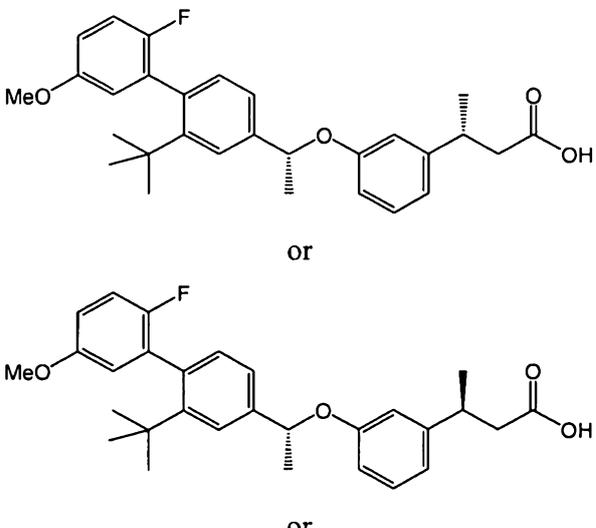
			
64.9	 or 	+++	ND
64.10	 or 	+++	+++
64.11	 or 	+++	+++

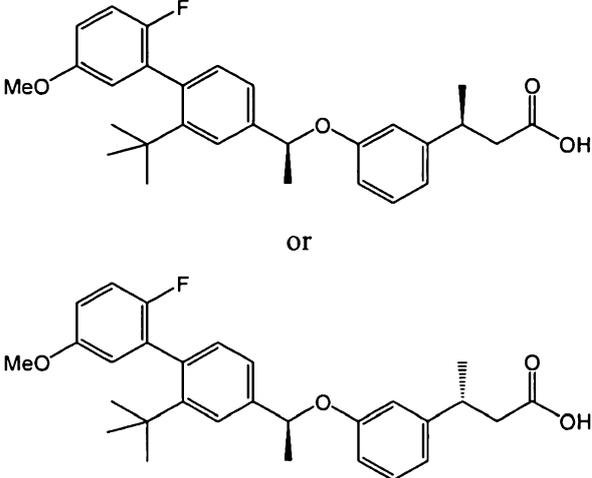
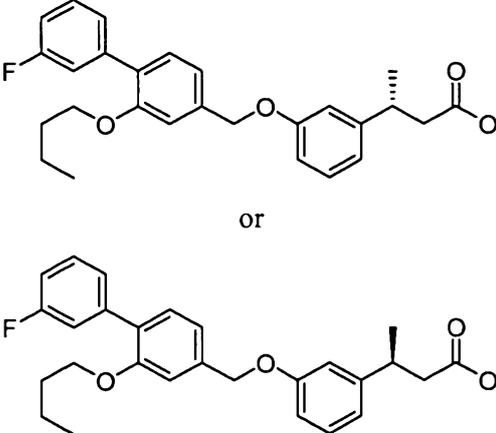
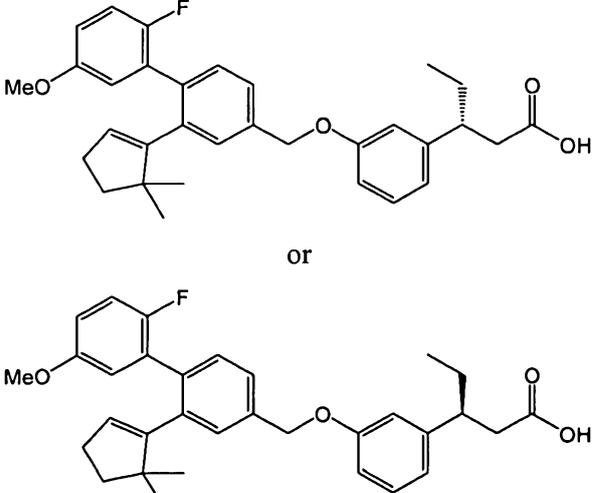
64.12	<p style="text-align: center;">or</p>	+++	++++
64.13	<p style="text-align: center;">or</p>	+++	++++
64.14		+++	+++

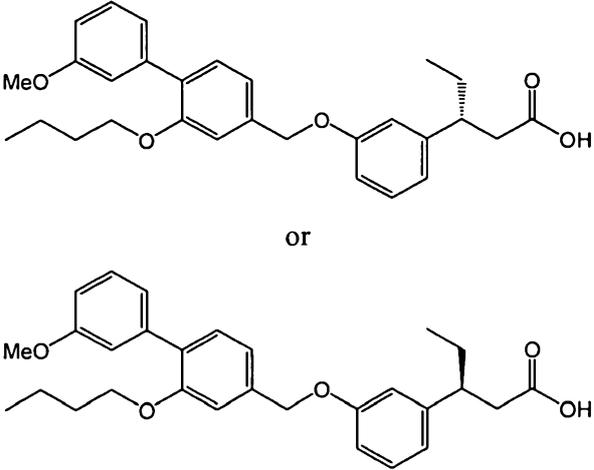
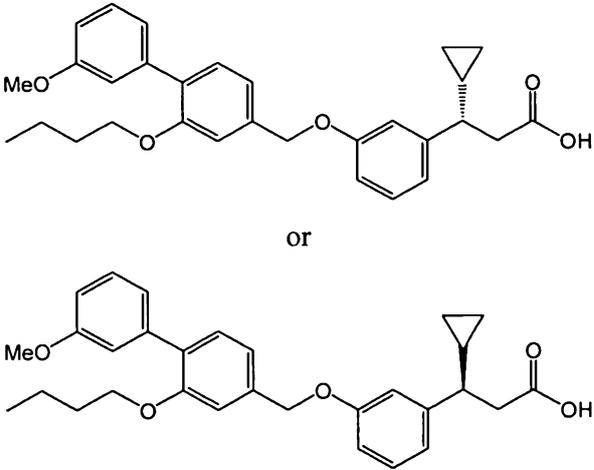
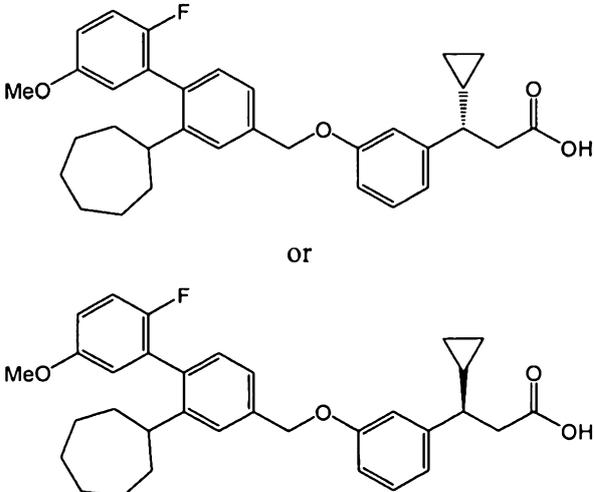
	<p>or</p> 		
64.15	 <p>or</p> 	+++	++++
64.16	 <p>or</p> 	+++	++++

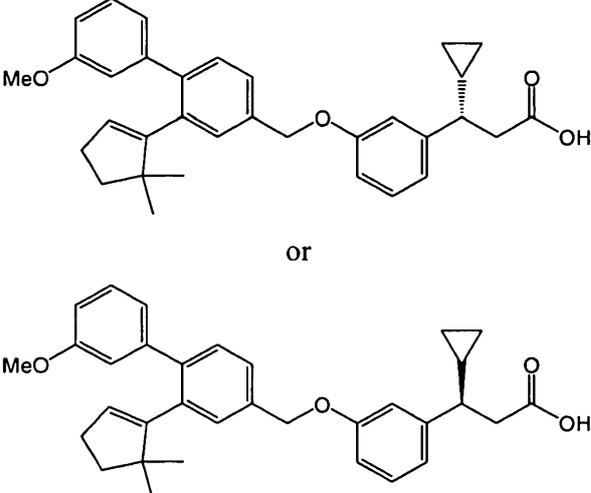
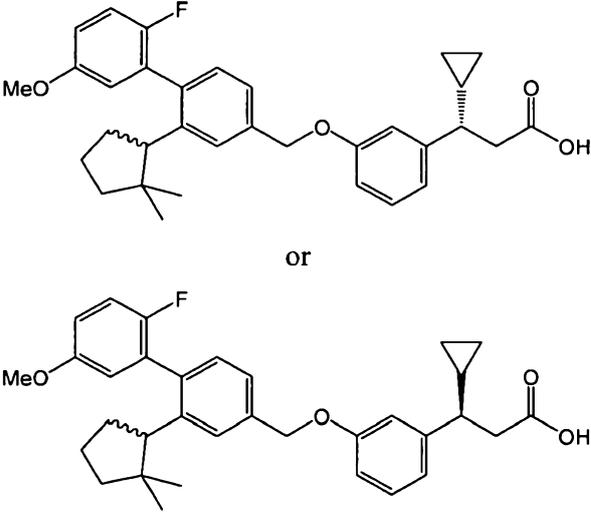
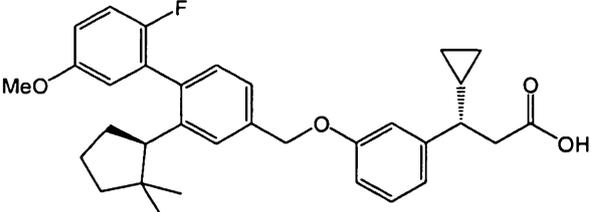
<p>64.17</p>	 <p>or</p>	<p>+++</p>	<p>++++</p>
<p>64.18</p>	 <p>or</p>	<p>+++</p>	<p>+++</p>
<p>64.19</p>	 <p>or</p>	<p>+++</p>	<p>+++</p>

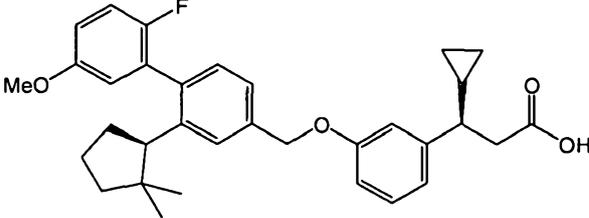
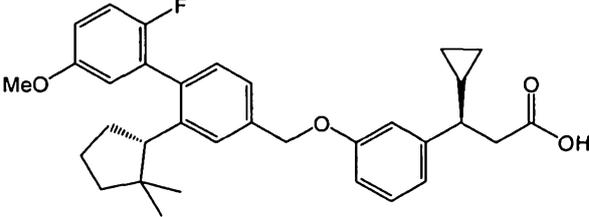
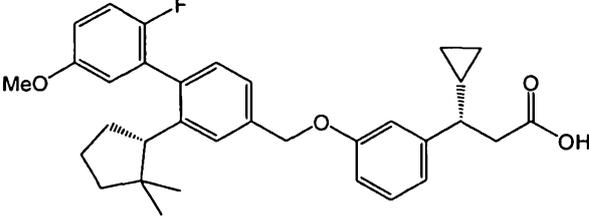
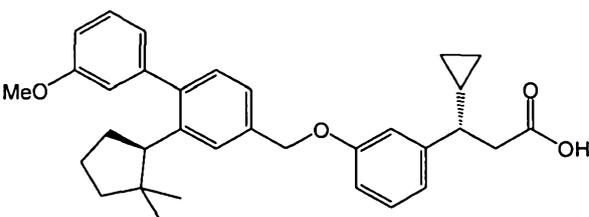
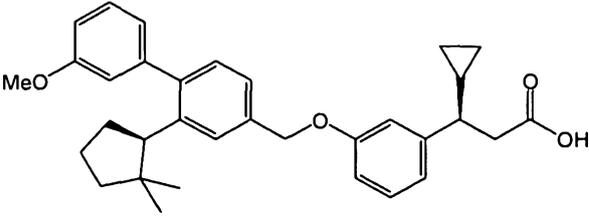
<p>64.20</p>	 <p>or</p>	<p>+++</p>	<p>++++</p>
<p>64.21</p>	 <p>or</p>	<p>+++</p>	<p>++++</p>
<p>64.22</p>	 <p>or</p>	<p>+++</p>	<p>++++</p>

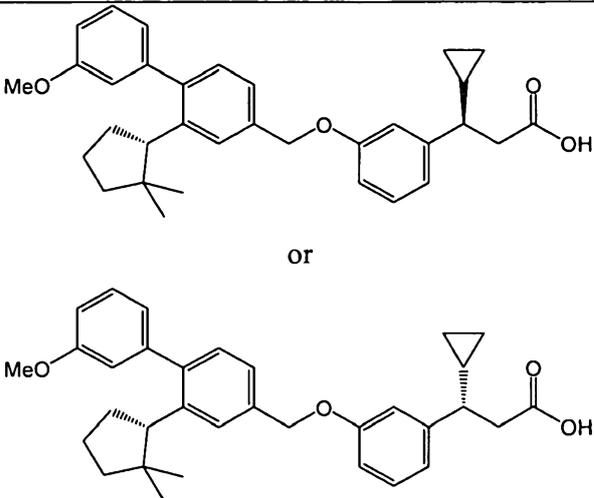
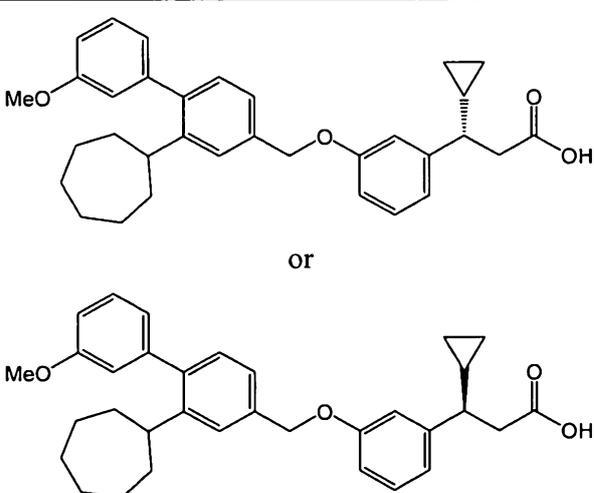
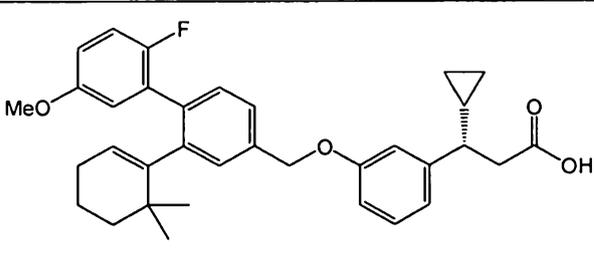
<p>64.23</p>	 <p>or</p>	<p>++</p>	<p>ND</p>
<p>64.24</p>	 <p>or</p>	<p>++</p>	<p>ND</p>
<p>64.25</p>	 <p>or</p>	<p>++</p>	<p>ND</p>

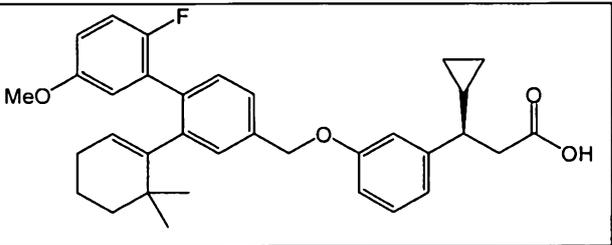
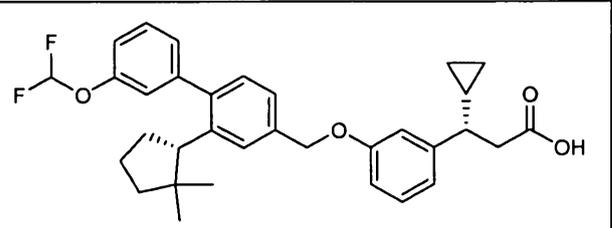
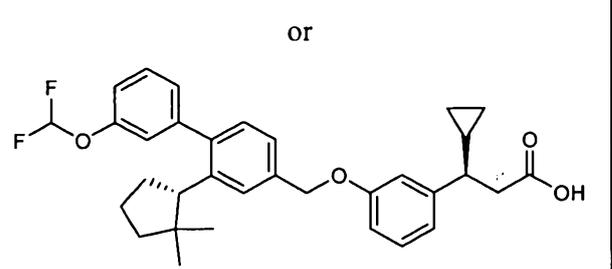
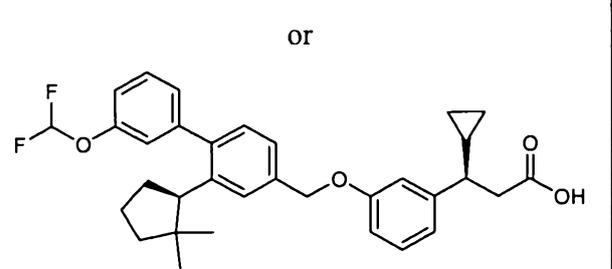
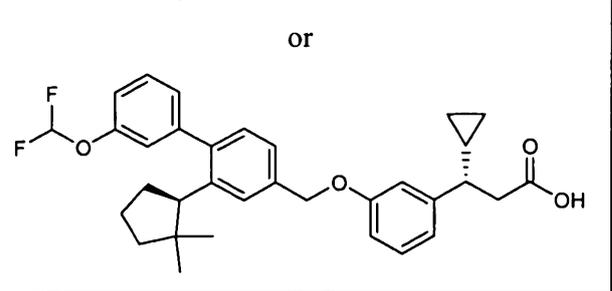
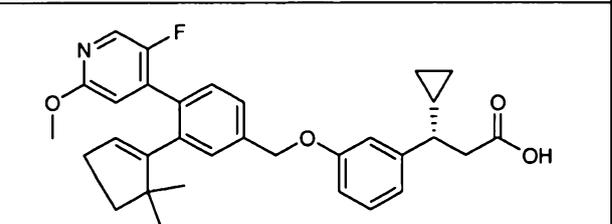
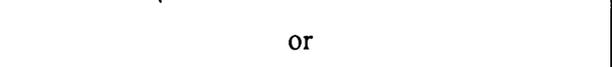
	 <p style="text-align: center;">or</p>		
<p>64.26</p>	 <p style="text-align: center;">or</p>	<p style="text-align: center;">++</p>	<p style="text-align: center;">ND</p>
<p>65.1</p>	 <p style="text-align: center;">or</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">++++</p>

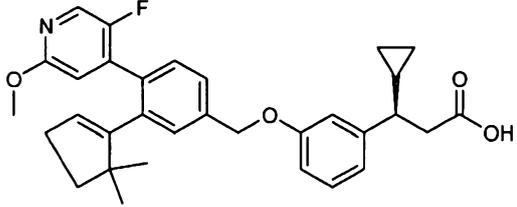
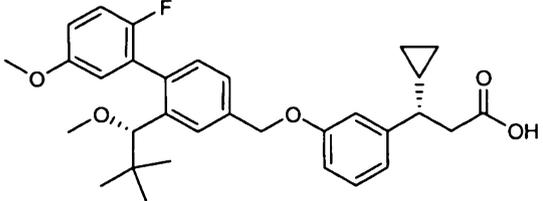
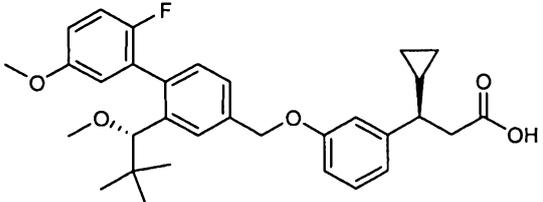
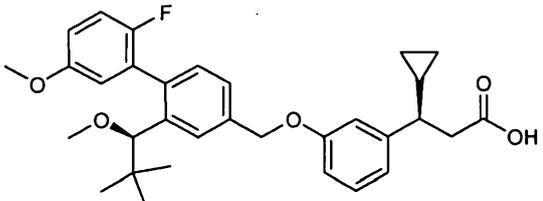
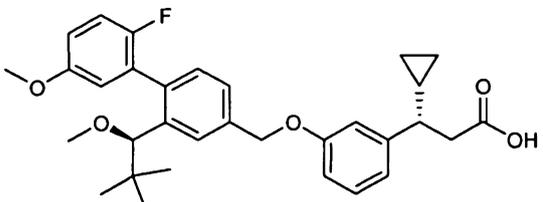
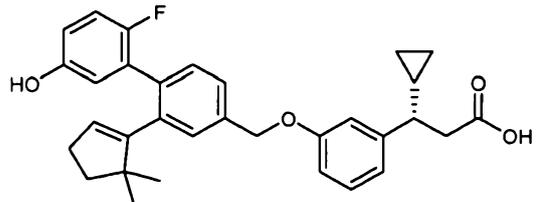
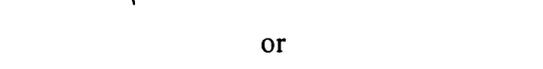
<p>65.2</p>		<p>+++</p>	<p>ND</p>
<p>66.1</p>		<p>+++</p>	<p>ND</p>
<p>66.2</p>		<p>+++</p>	<p>++++</p>

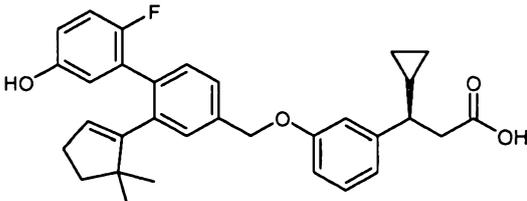
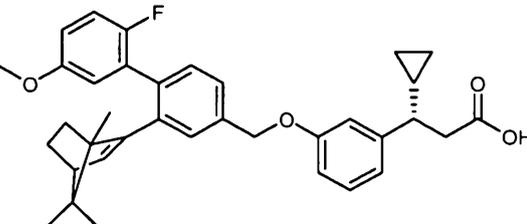
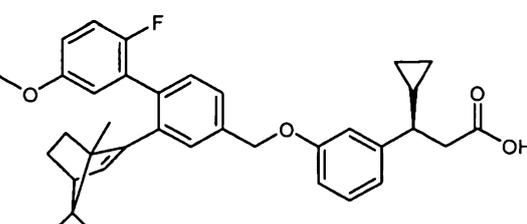
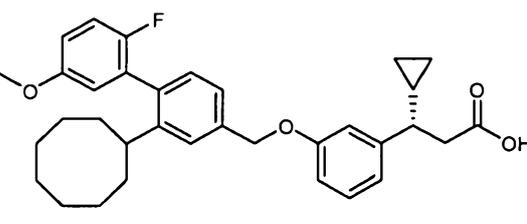
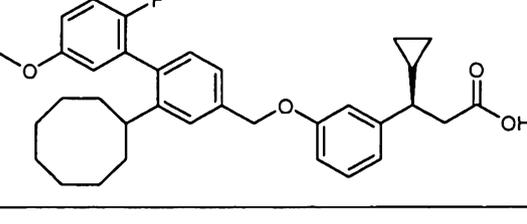
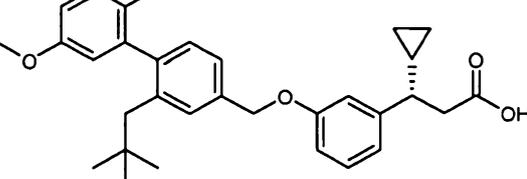
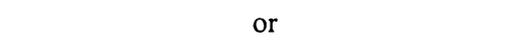
<p>66.3</p>	 <p>or</p>	<p>+++ / ++++</p>	<p>+++++</p>
<p>66.4</p>	 <p>or</p>	<p>+++</p>	<p>+++++</p>
<p>66.5</p>	 <p>or</p>	<p>+++</p>	<p>ND</p>

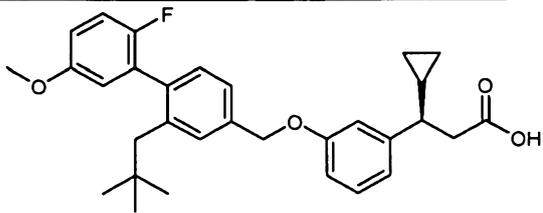
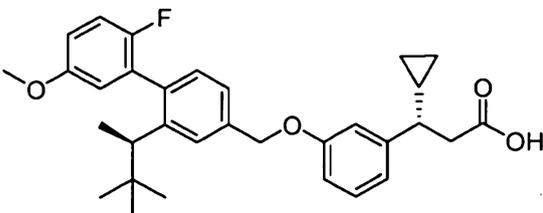
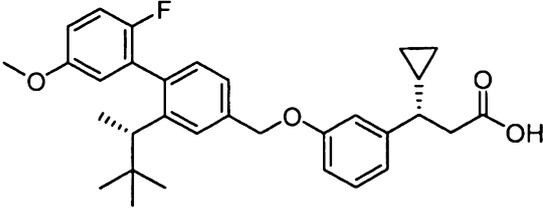
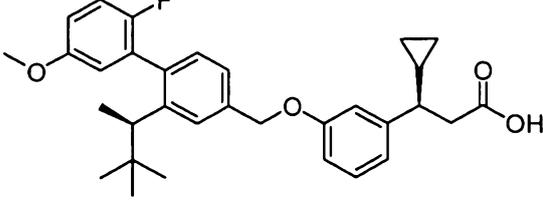
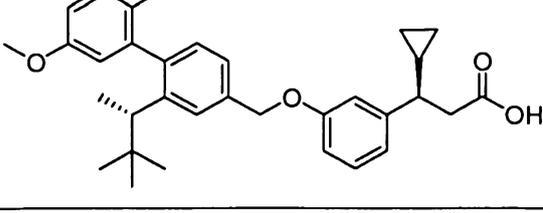
	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 		
<p>66.6</p>	<p style="text-align: center;">Diastereomer of 66.5</p>	<p style="text-align: center;">++++</p>	<p style="text-align: center;">+++++</p>
<p>66.7</p>	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">ND</p>

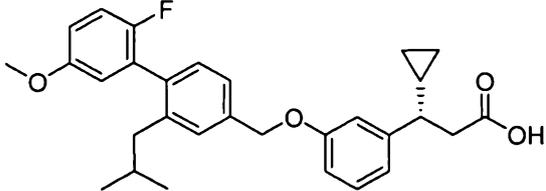
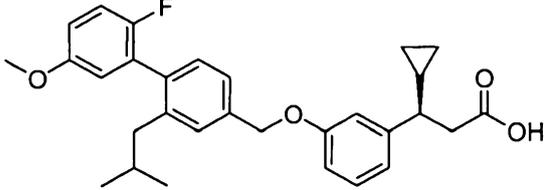
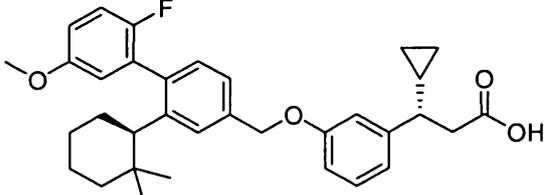
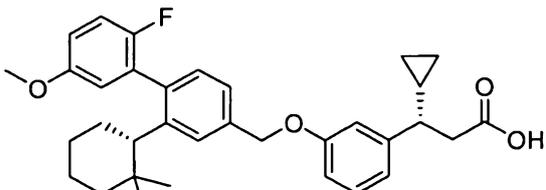
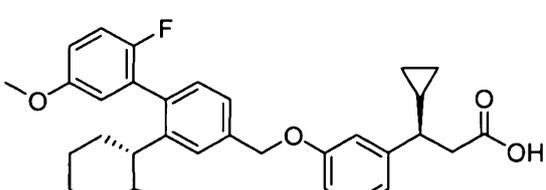
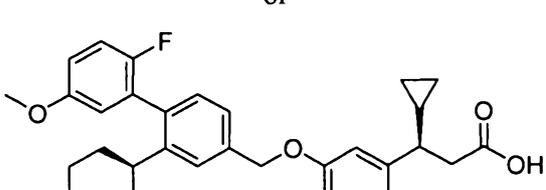
	 <p style="text-align: center;">or</p>		
<p>66.8</p>	<p style="text-align: center;">Diastereomer of 66.7</p>	<p style="text-align: center;">++++</p>	<p style="text-align: center;">+++++</p>
<p>66.9</p>	 <p style="text-align: center;">or</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">+++++</p>
<p>66.10</p>	 <p style="text-align: center;">or</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">+++++</p>

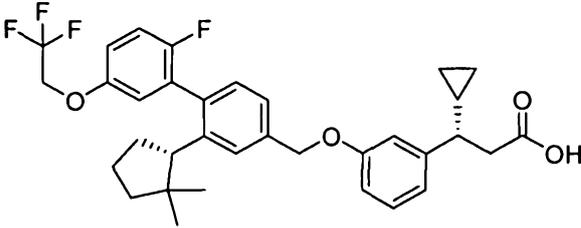
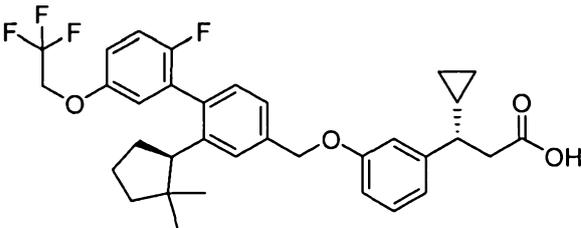
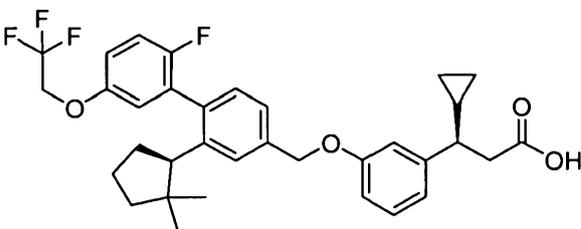
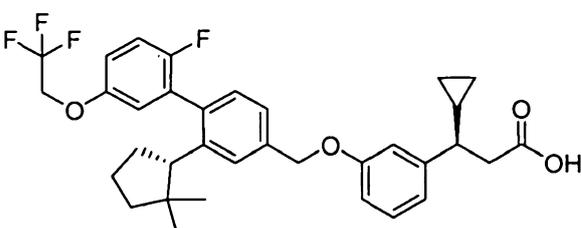
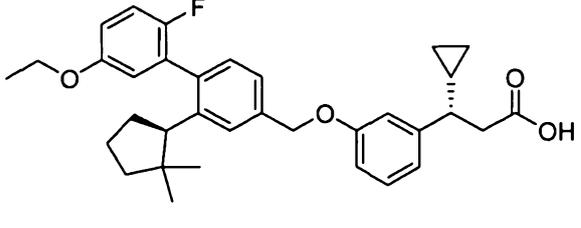
			
<p>66.11</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>+++</p>	<p>++++</p>
<p>66.12</p>	 <p>or</p> 	<p>+++</p>	<p>++++</p>

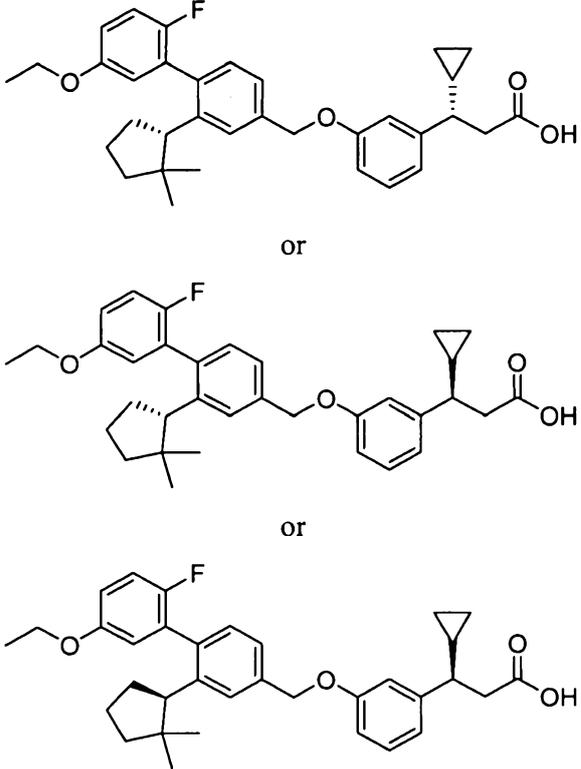
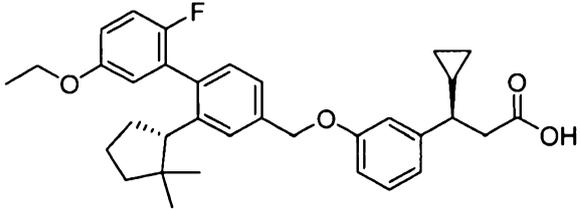
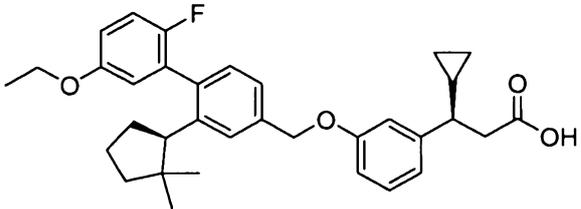
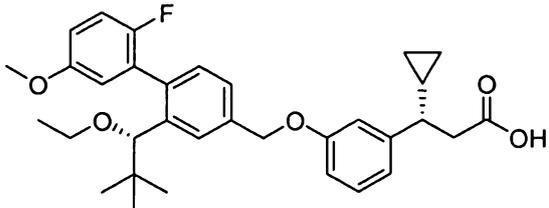
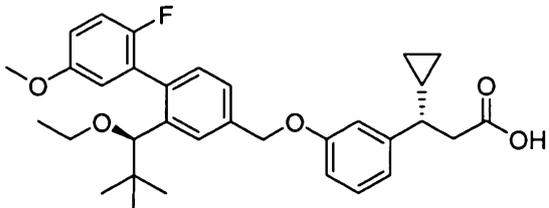
			
<p>66.13</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>+++</p>	<p>+++++</p>
<p>66.14</p>	 <p>or</p> 	<p>+++</p>	<p>ND</p>

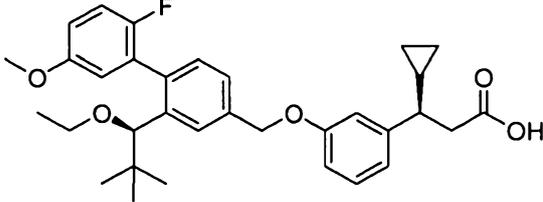
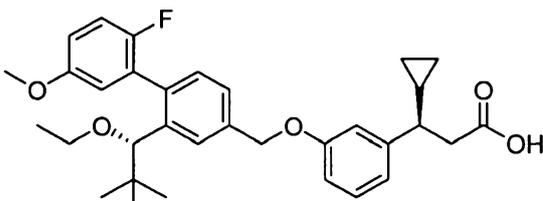
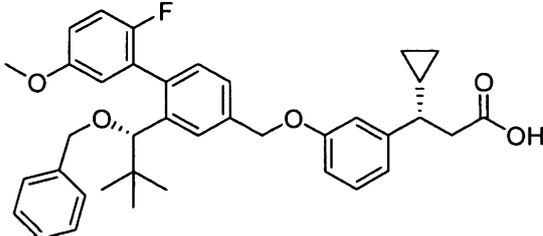
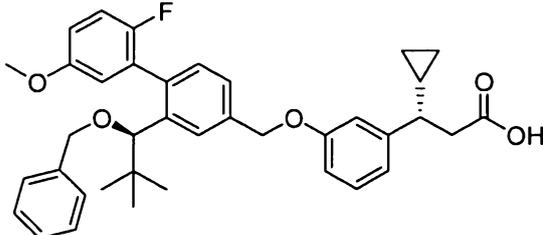
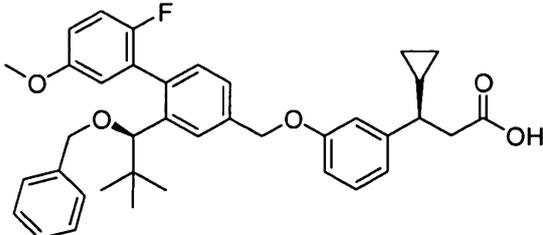
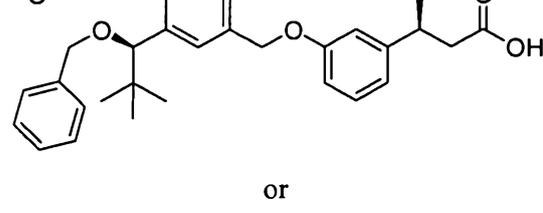
			
66.15	 or 	+++	+++++
66.16	 or 	+++	ND
66.17	 or 	++++	+++++

			
66.18	 or  or  or 	+++	ND
66.19	Diastereomer of 66.18	++++	+++++

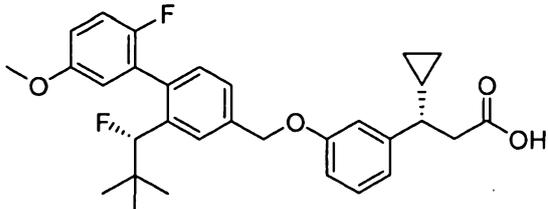
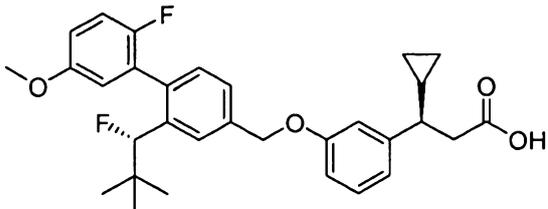
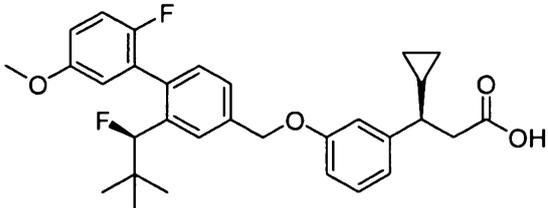
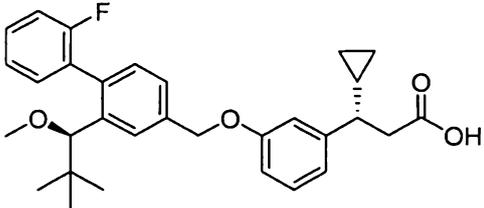
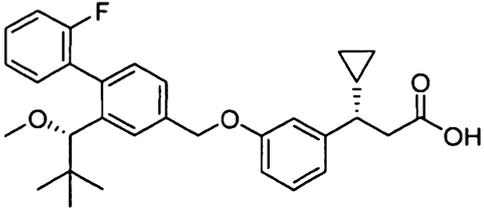
<p>66.20</p>	 <p>or</p> 	<p>+++</p>	<p>++++</p>
<p>66.21</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>+++</p>	<p>ND</p>

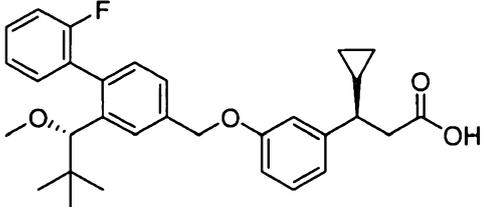
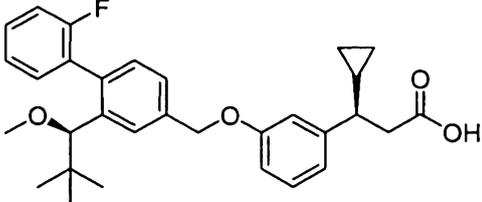
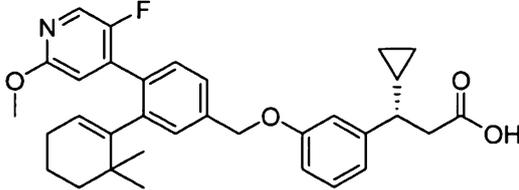
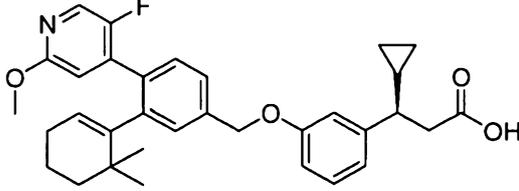
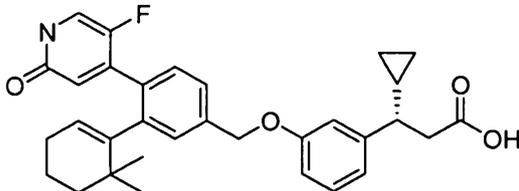
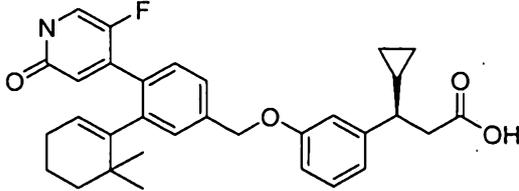
66.22	Diastereomer of 66.21	++++	+++++
66.23	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	++	ND
66.24	Diastereomer of 66.13	++	+++
66.25	 <p style="text-align: center;">or</p>	++	++

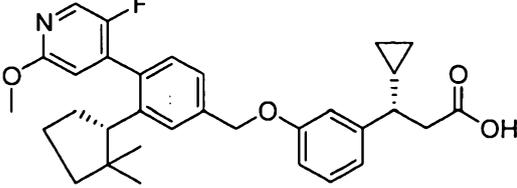
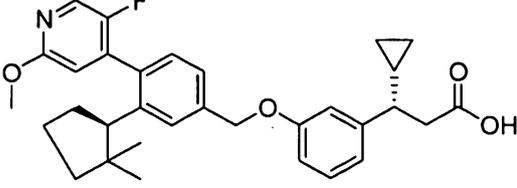
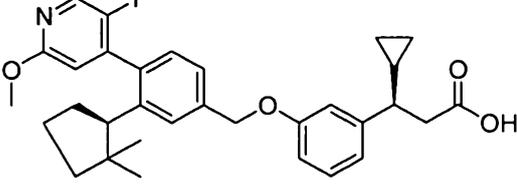
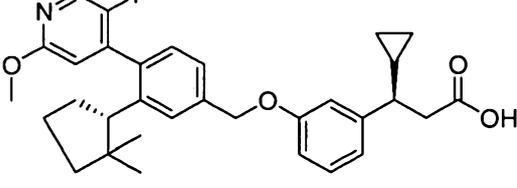
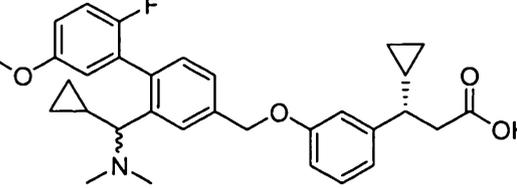
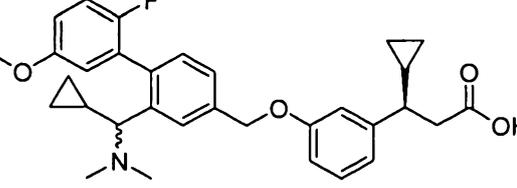
	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 		
<p>66.26</p>	<p style="text-align: center;">Diastereomer of 66.25</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">++++</p>
<p>66.27</p>	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">+++++</p>

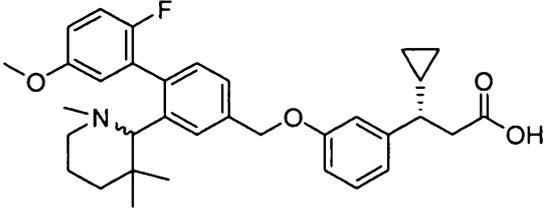
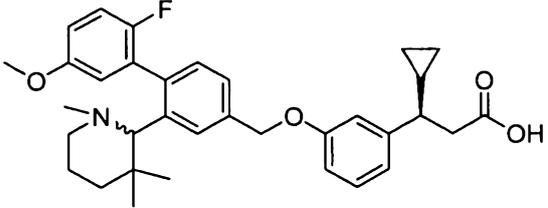
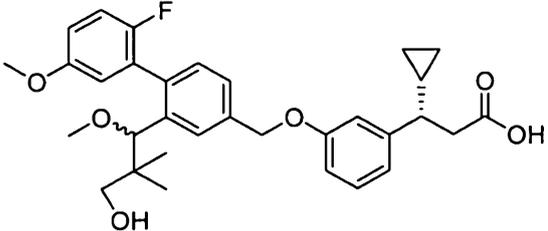
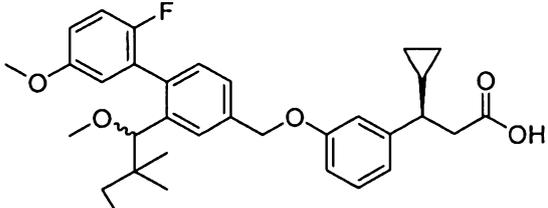
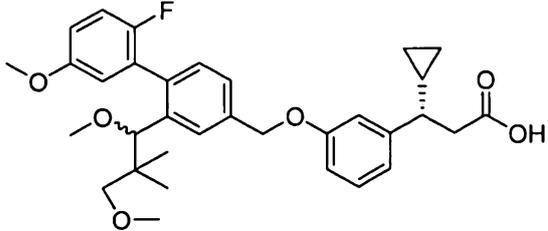
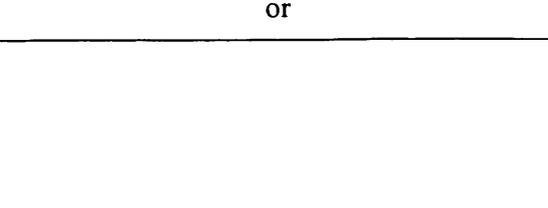
	 <p style="text-align: center;">or</p> 		
<p>66.28</p>	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	<p style="text-align: center;">+++</p>	<p style="text-align: center;">+++++</p>

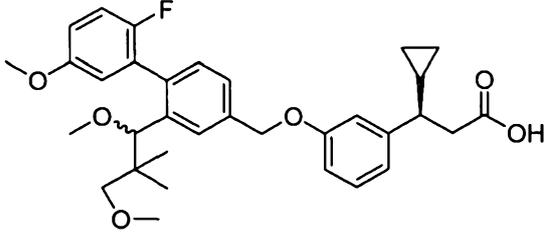
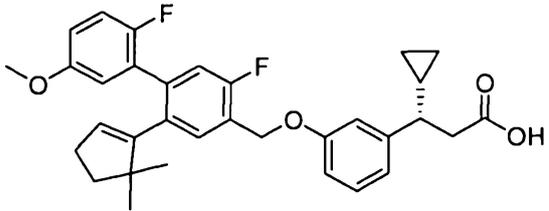
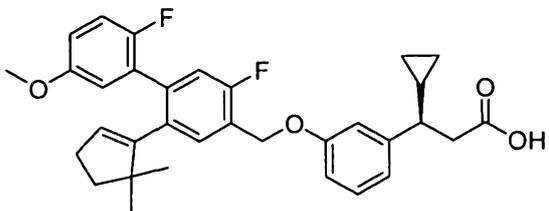
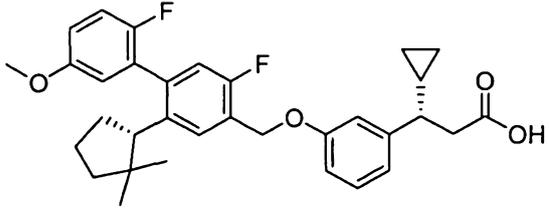
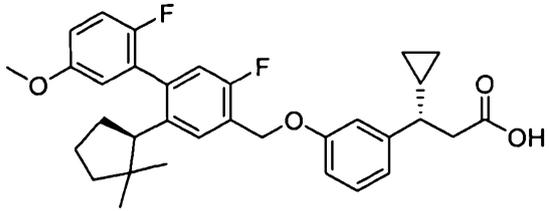
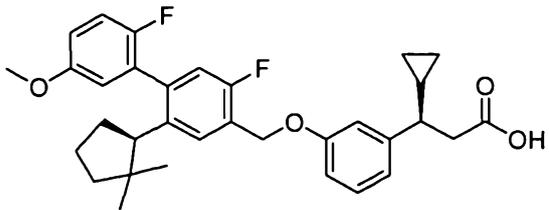
66.29	<p>or</p> <p>or</p> <p>or</p>	+++	ND
66.30		+++	ND

	<p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 		
<p>66.31</p>	<p style="text-align: center;">Diastereomer of 66.30</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">++++</p>
<p>66.32</p>	<p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">ND</p>

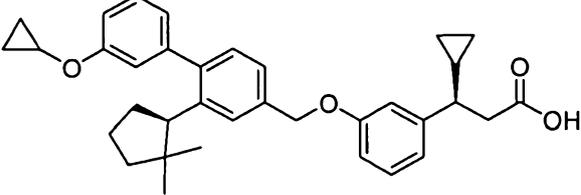
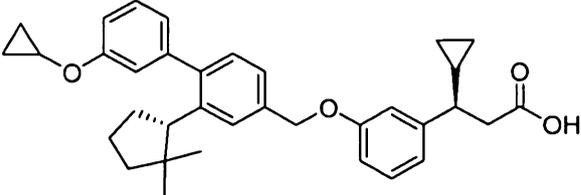
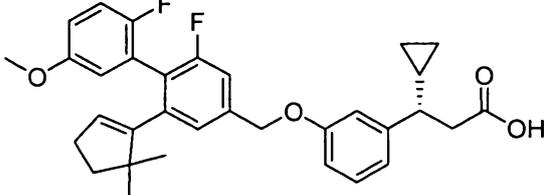
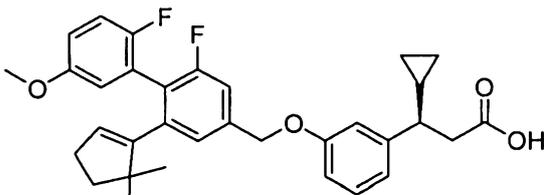
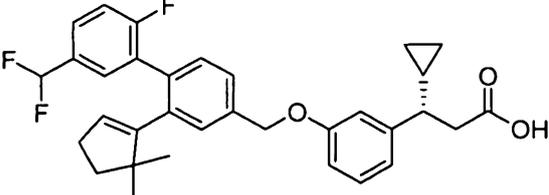
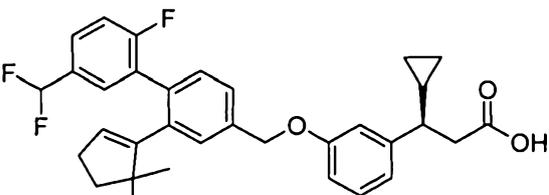
	 <p style="text-align: center;">or</p> 		
66.33	Diastereomer of 66.32	+++	++++
66.34	 <p style="text-align: center;">or</p> 	++++	++++
66.35	 <p style="text-align: center;">or</p> 	++	ND

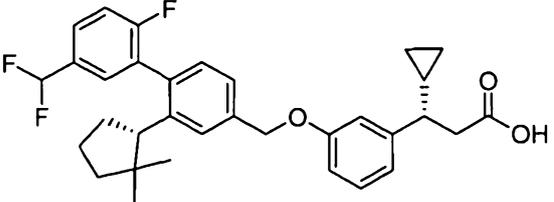
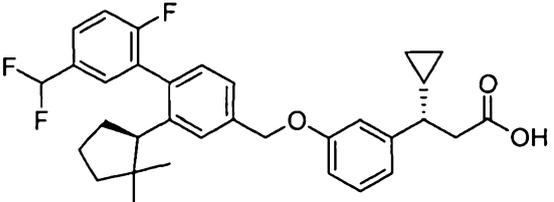
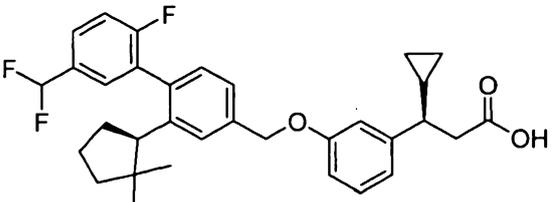
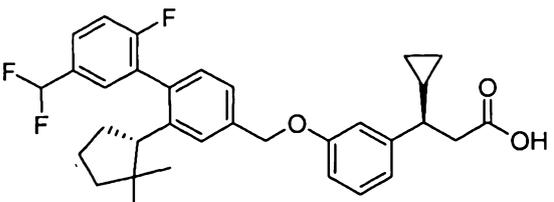
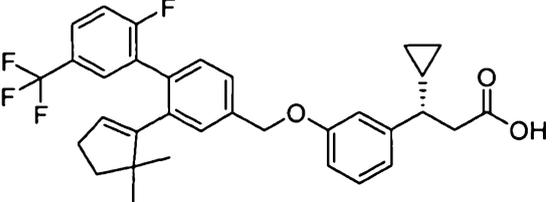
<p>66.36</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>++++</p>	<p>+++++</p>
<p>66.37</p>	<p>Diastereomer of 66.36</p>	<p>+++</p>	<p>++++</p>
<p>66.38</p>	 <p>or</p> 	<p>++</p>	<p>ND</p>

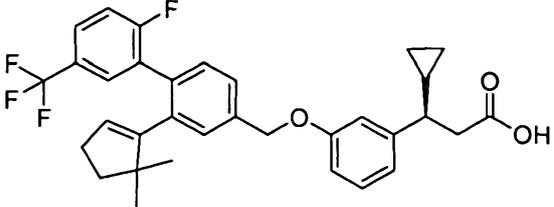
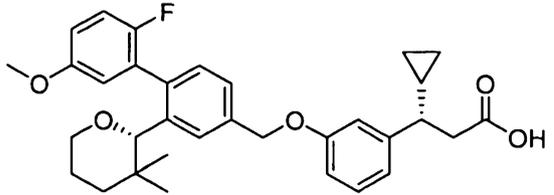
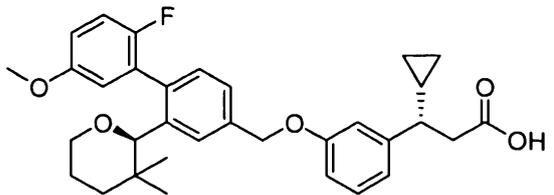
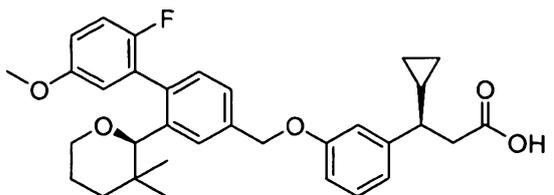
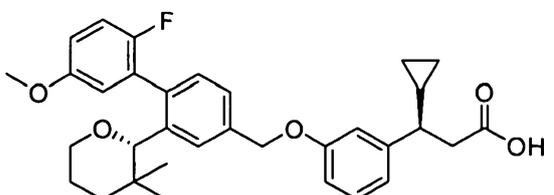
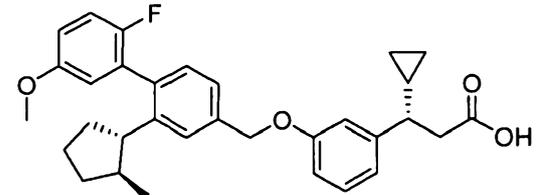
<p>66.39</p>	<p>No compound associated with this number</p>		
<p>66.40</p>	 <p>or</p> 	<p>+++</p>	<p>++++</p>
<p>66.41</p>	 <p>or</p> 	<p>+++</p>	<p>ND</p>
<p>66.42</p>	 <p>or</p> 	<p>+++</p>	<p>++++</p>

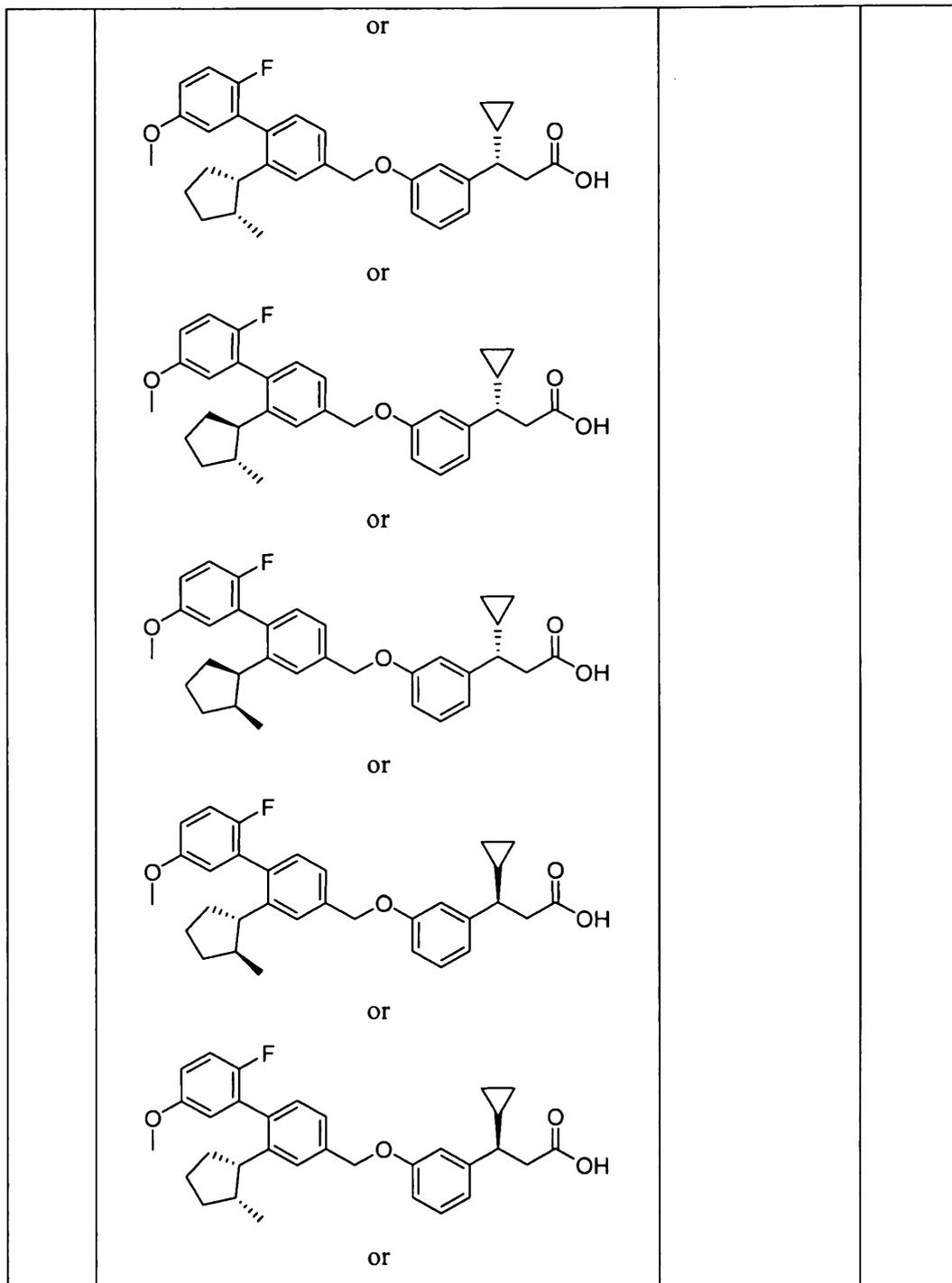
			
<p>66.43</p>	 <p style="text-align: center;">or</p> 	<p style="text-align: center;">+++</p>	<p style="text-align: center;">+++++</p>
<p>66.44</p>	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	<p style="text-align: center;">++++</p>	<p style="text-align: center;">+++++</p>

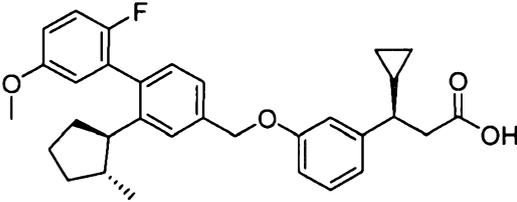
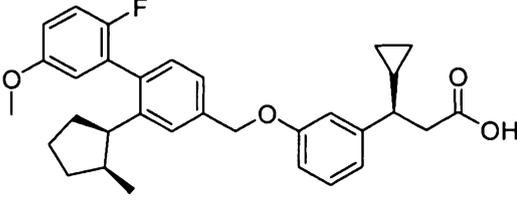
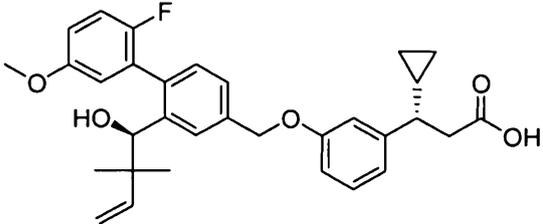
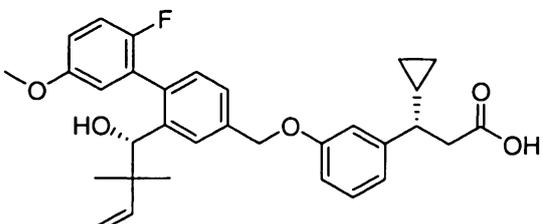
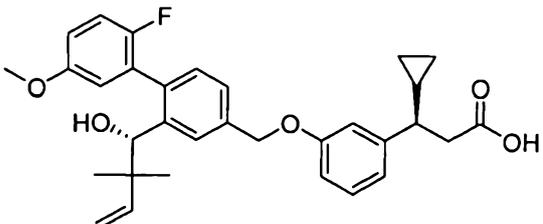
	<p>or</p>		
66.45	Diastereomer of 66.44	+++	ND
66.46	<p>or</p>	++	ND
	66.47	Diastereomer of 66.11	+++
66.48	<p>or</p> <p>or</p>	+++	ND

	 <p style="text-align: center;">or</p> 		
<p>66.49</p>	 <p style="text-align: center;">or</p> 	<p style="text-align: center;">+++</p>	<p style="text-align: center;">++++</p>
<p>66.50</p>	 <p style="text-align: center;">or</p> 	<p style="text-align: center;">+++</p>	<p style="text-align: center;">+++</p>

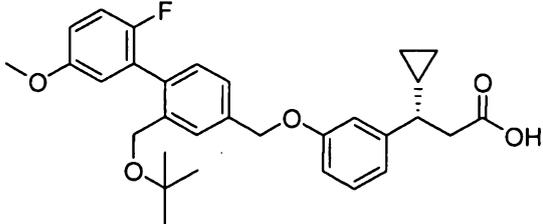
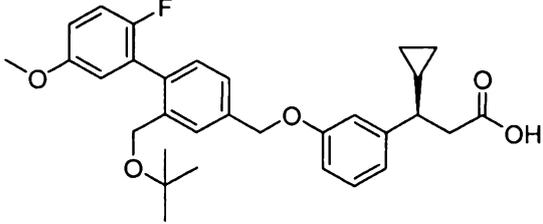
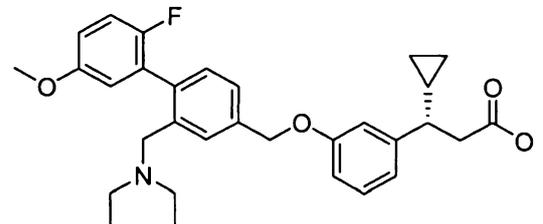
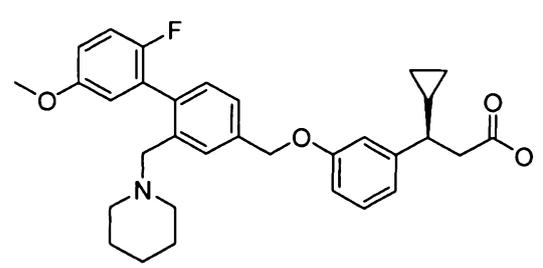
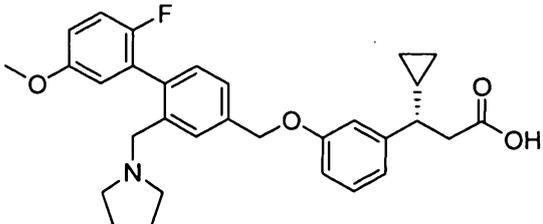
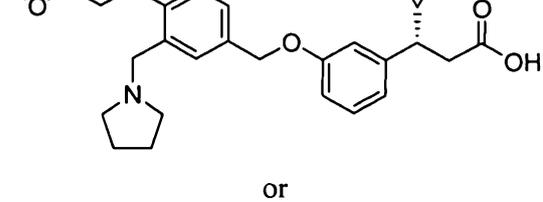
<p>66.51</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>+++</p>	<p>++++</p>
<p>66.52</p>	<p>Diastereomer of 66.51</p>	<p>++</p>	<p>ND</p>
<p>66.53</p>	 <p>or</p>	<p>++</p>	<p>ND</p>

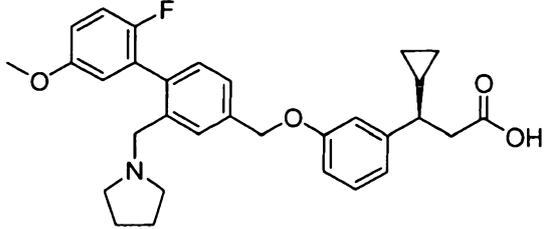
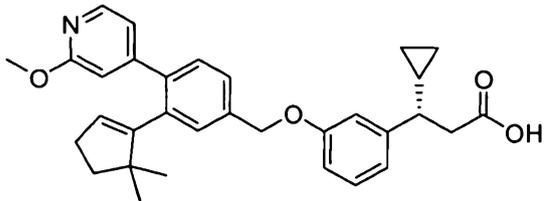
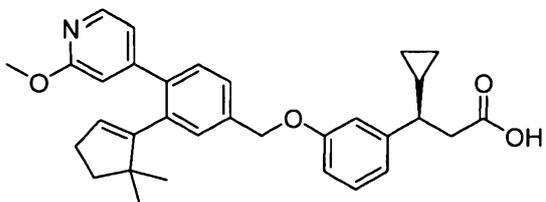
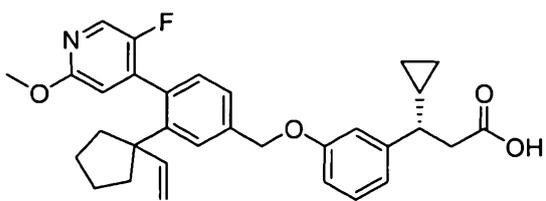
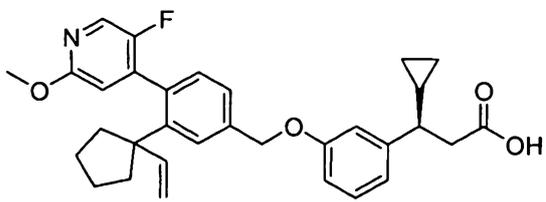
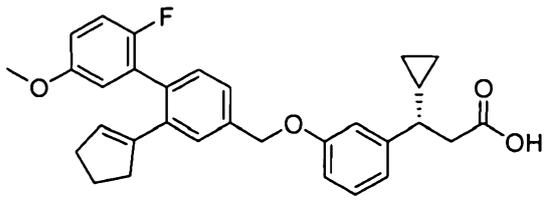
			
66.54	 or  or  or 	+++	++++
66.55	Diastereomer of 66.54	++	ND
66.56		+++	++++

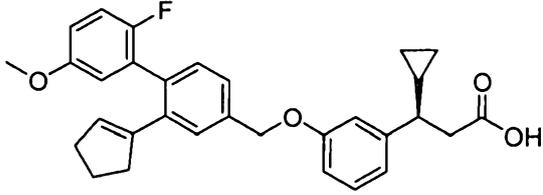
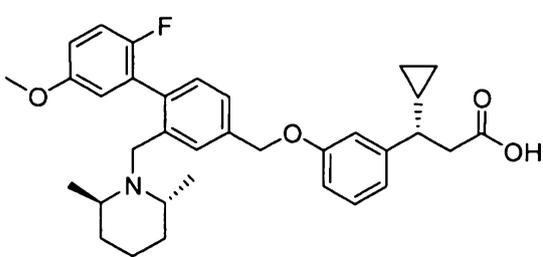
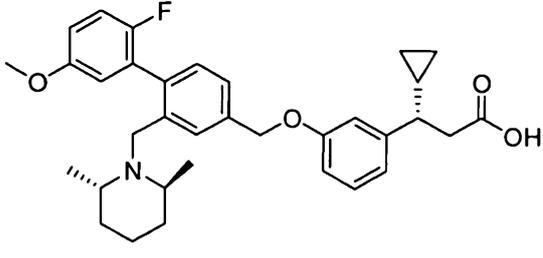
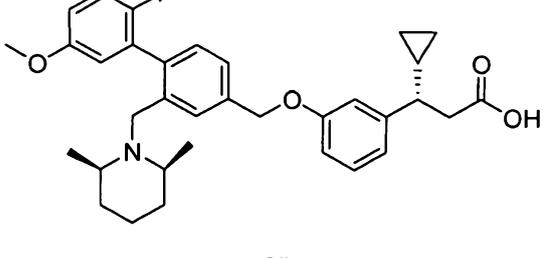
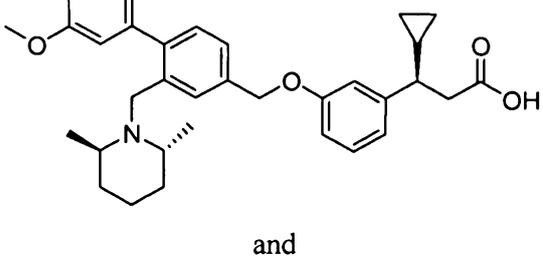


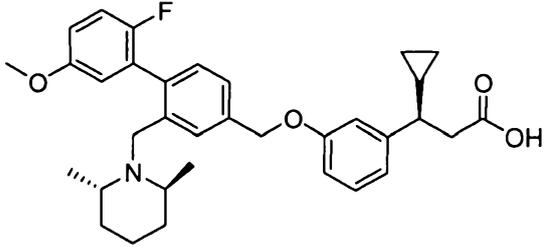
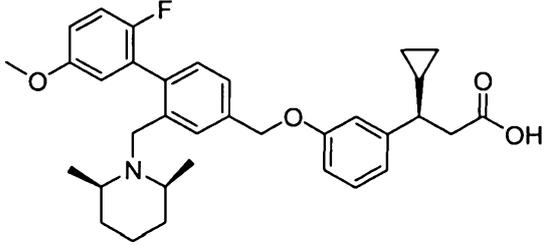
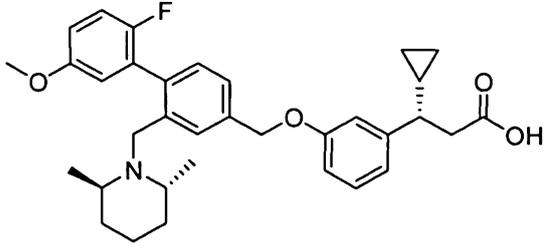
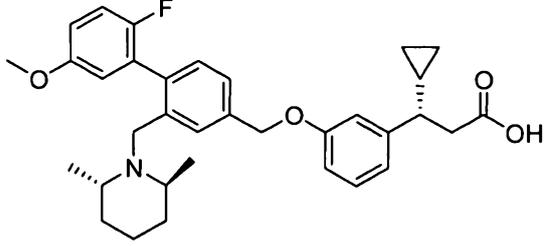
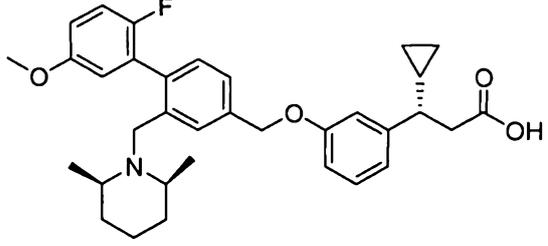
	 <p style="text-align: center;">or</p> 		
66.57	Diastereomer of 66.56	+++	+++++
66.58	Diastereomer of 66.56 and 66.57,	+++	ND
66.59	Diastereomer of 66.56, 66.57, and 66.58	+++	ND
66.60	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	++	ND

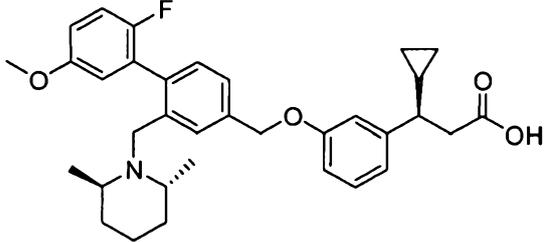
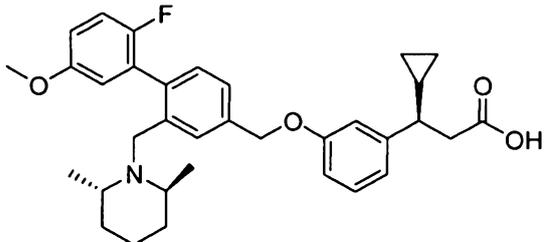
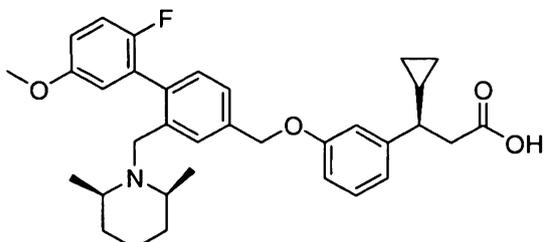
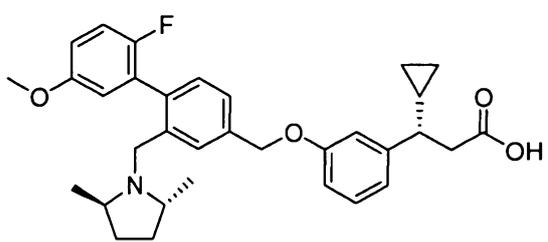
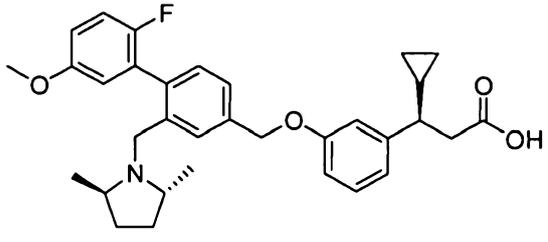
	<p>or</p>		
66.61	<p>Diastereomer of 66.60</p>	+++	ND
66.62	<p>or</p> <p>or</p> <p>or</p>	++++	+++++

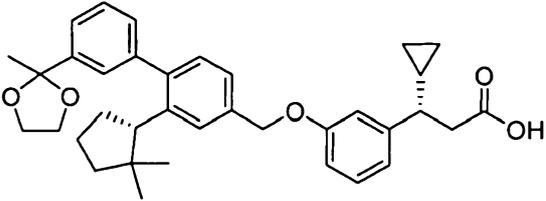
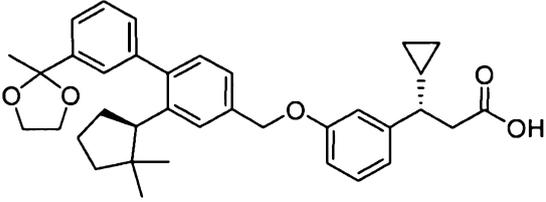
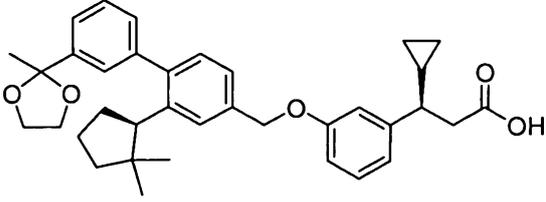
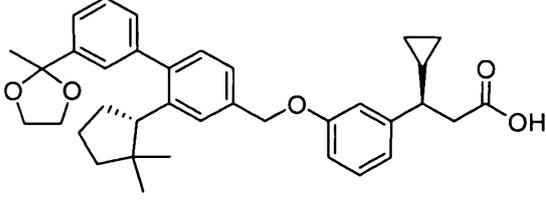
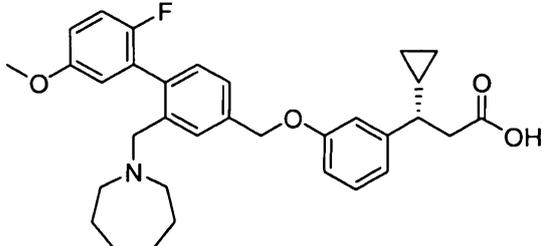
<p>66.63</p>	 <p>or</p> 	<p>++</p>	<p>++</p>
<p>66.64</p>	 <p>or</p> 	<p>++</p>	<p>ND</p>
<p>66.65</p>	 <p>or</p> 	<p>++</p>	<p>ND</p>

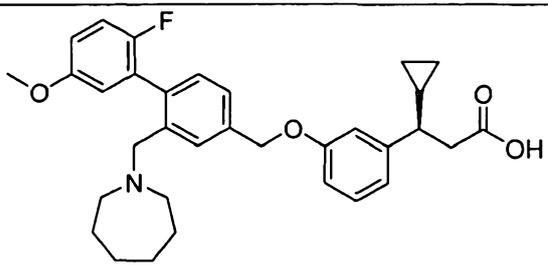
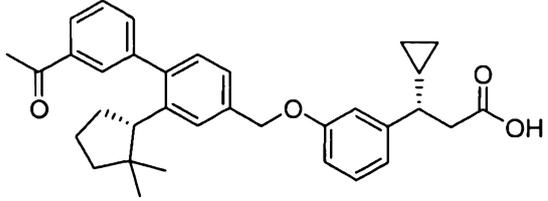
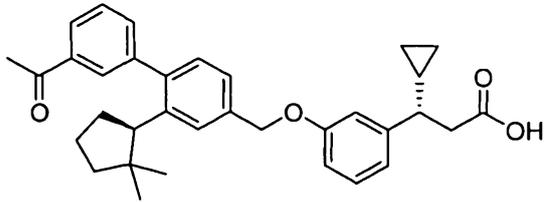
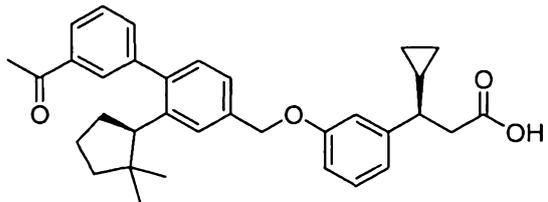
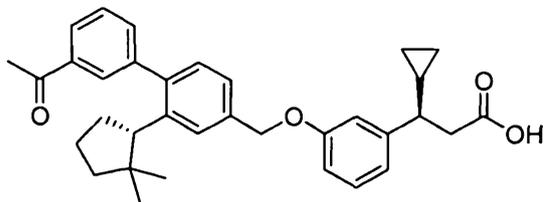
			
66.66	 or 	+++	++++
66.67	 or 	+++	++++
66.68	 or 	+++	++++

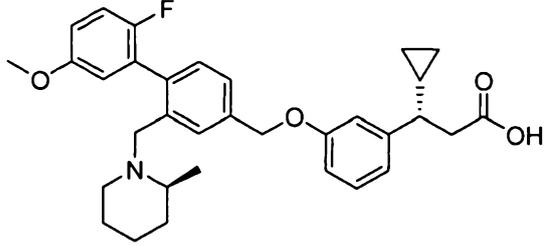
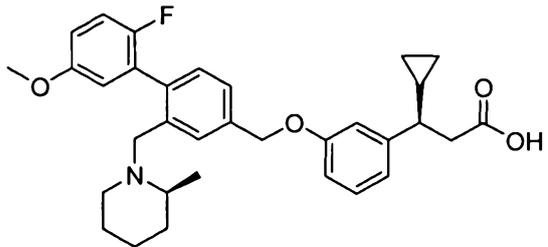
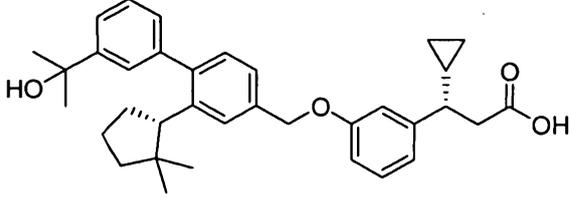
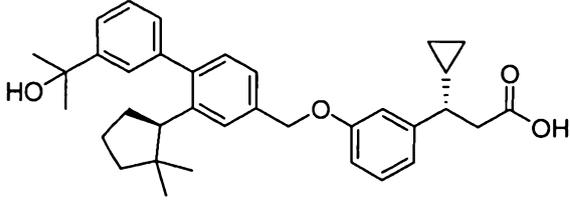
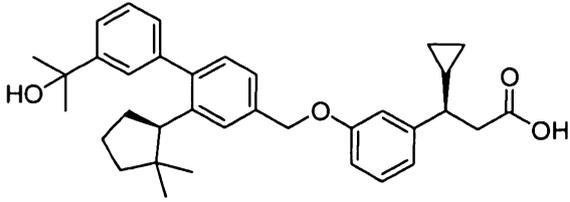
			
<p>66.69</p>			
	<p>and</p>		
			
	<p>or</p>		
			
<p>or</p>			
			
<p>and</p>			

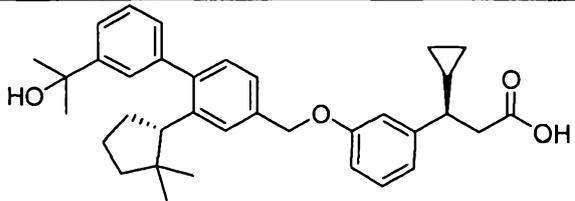
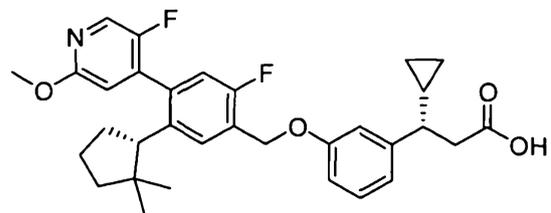
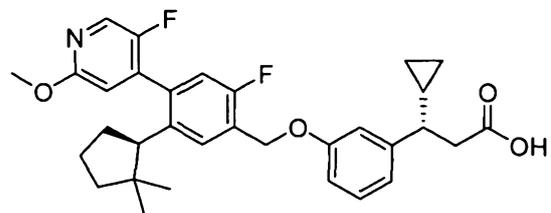
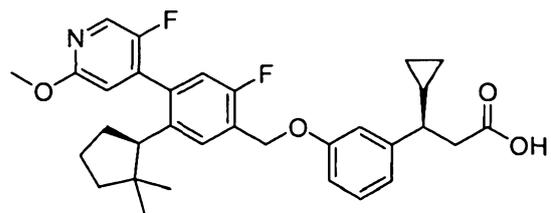
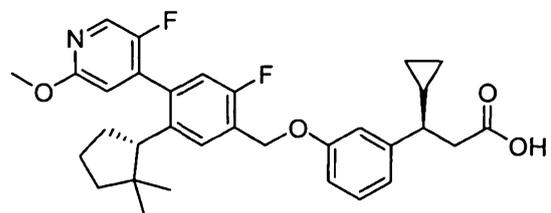
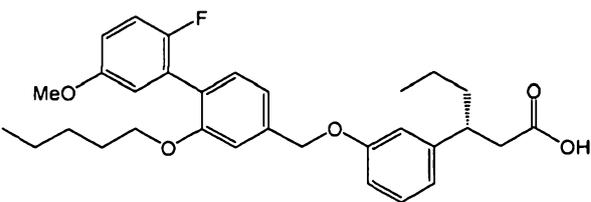
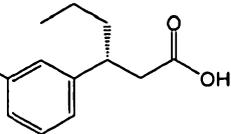
	 <p style="text-align: center;">or</p> 		
<p>66.70</p>	 <p style="text-align: center;">and</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">++++</p>

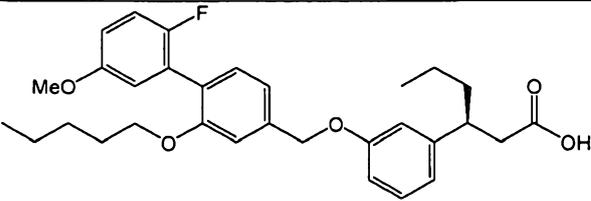
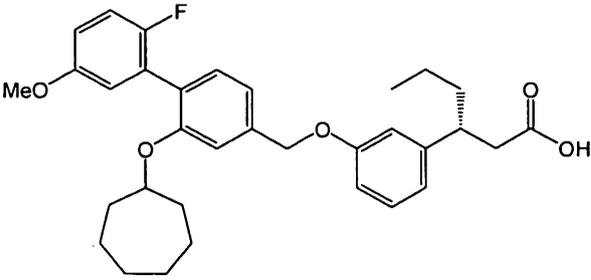
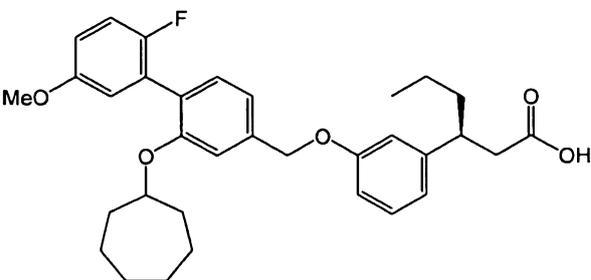
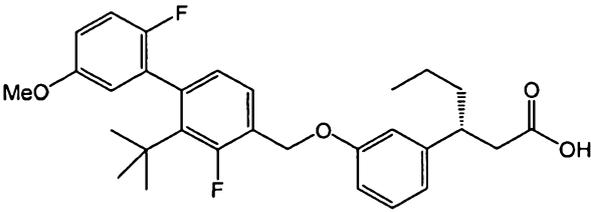
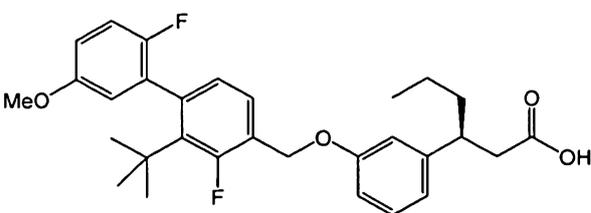
	 <p style="text-align: center;">and</p>  <p style="text-align: center;">or</p>  <p>but not the same one as 66.69</p>		
<p>66.71</p>	 <p style="text-align: center;">or</p> 	<p style="text-align: center;">+++</p>	<p style="text-align: center;">+++</p>

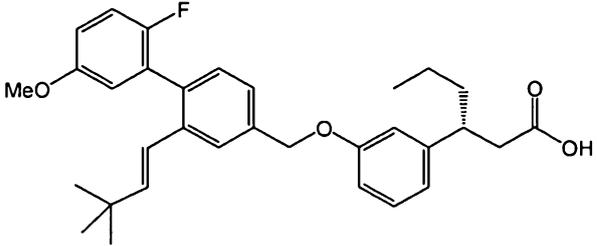
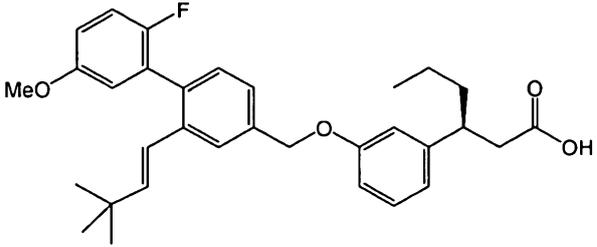
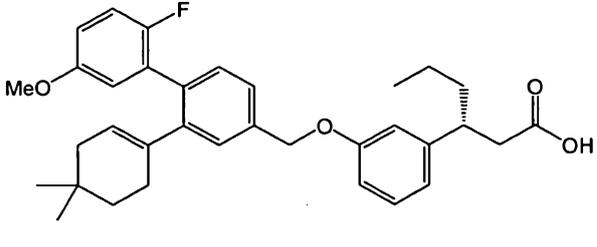
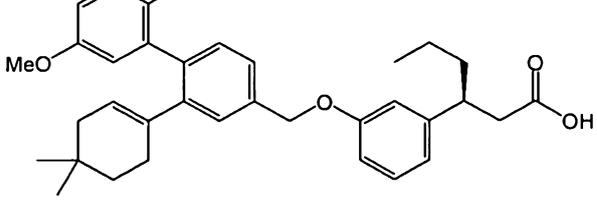
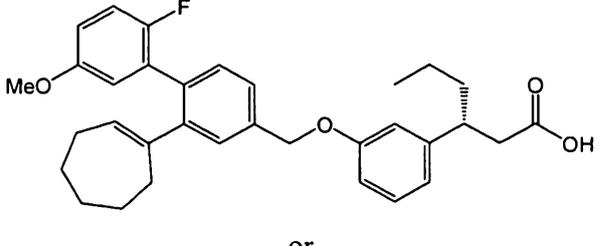
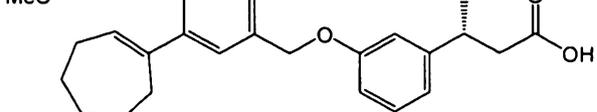
<p>66.72</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>++</p>	<p>ND</p>
<p>66.73</p>	 <p>or</p>	<p>++</p>	<p>ND</p>

			
<p>66.74</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>++</p>	<p>ND</p>

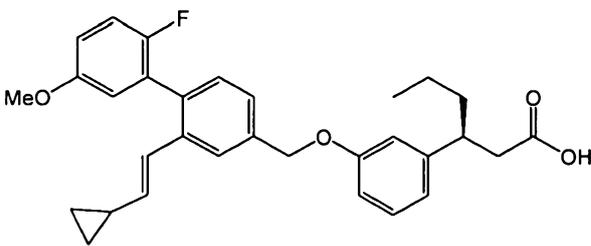
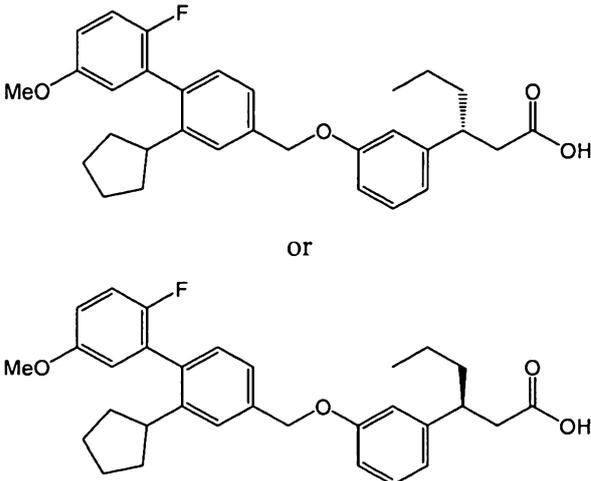
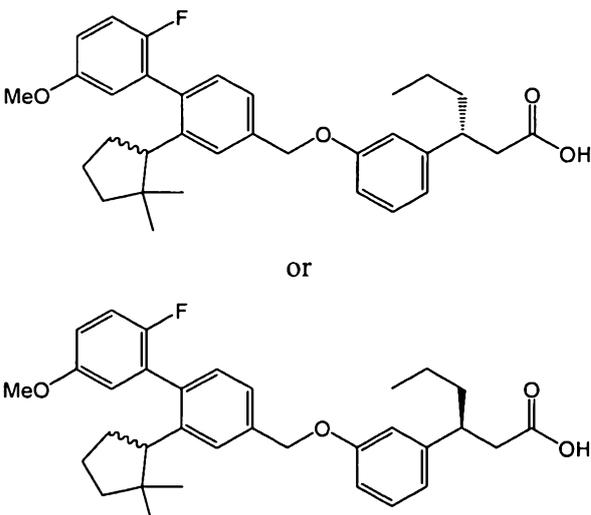
<p>66.75</p>	 <p>or</p> 	<p>++</p>	<p>ND</p>
<p>66.76</p>	 <p>or</p>  <p>or</p> 	<p>++</p>	<p>ND</p>

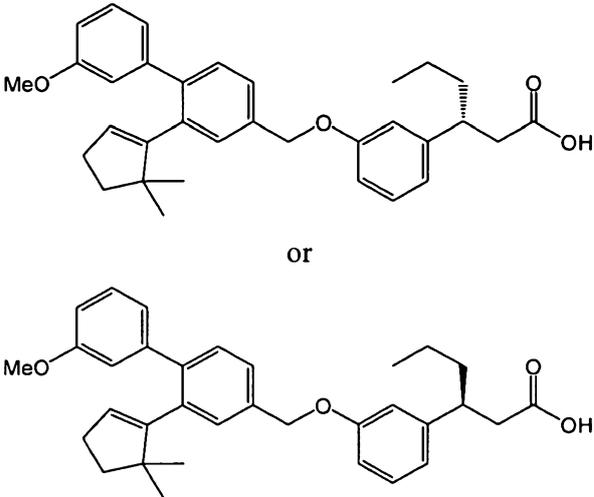
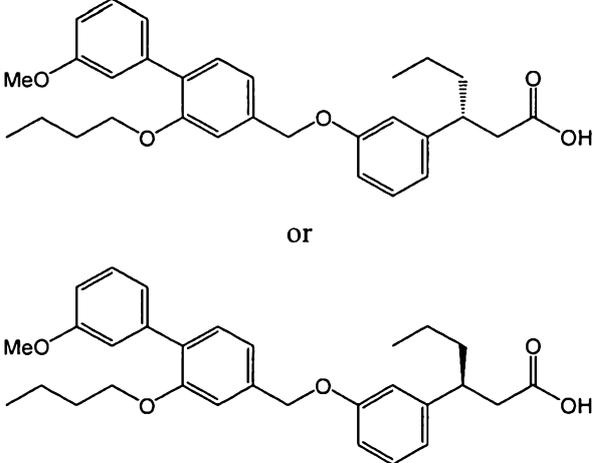
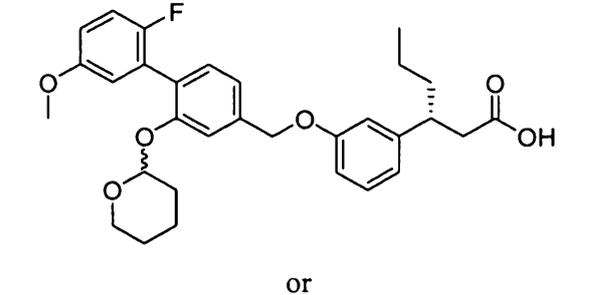
			
66.77	 or  or  or 	++++	+++++
67.1	 or 	+++	ND

			
67.2	 <p style="text-align: center;">or</p> 	+++	+++
67.3	 <p style="text-align: center;">or</p> 	+++	ND

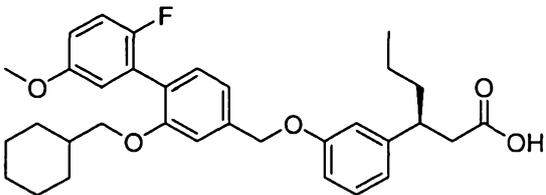
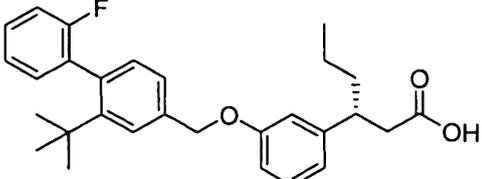
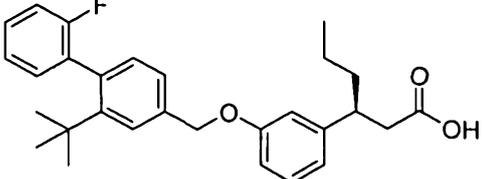
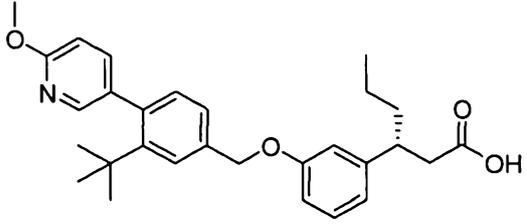
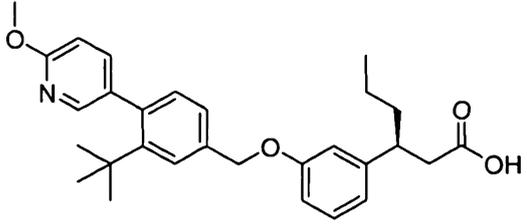
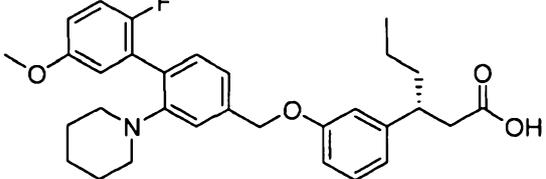
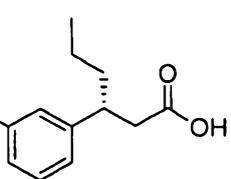
<p>67.4</p>	 <p>or</p> 	<p>+++</p>	<p>ND</p>
<p>67.5</p>	 <p>or</p> 	<p>+++</p>	<p>ND</p>
<p>67.6</p>	 <p>or</p> 	<p>+++</p>	<p>++++</p>

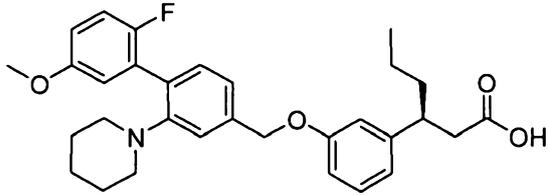
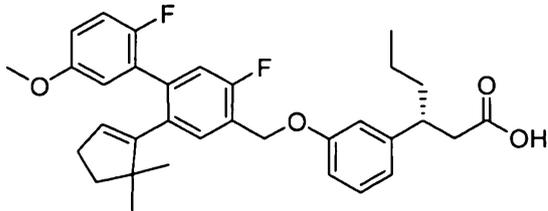
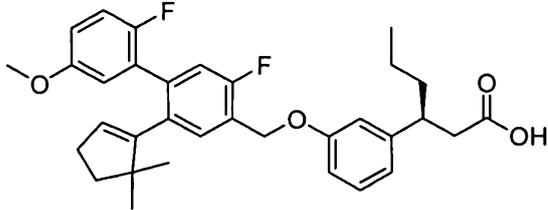
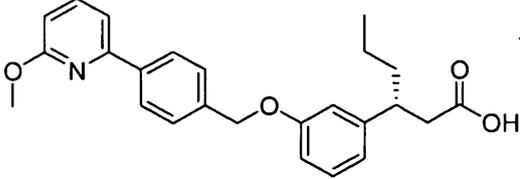
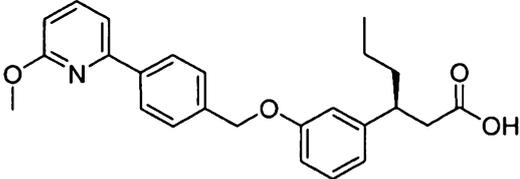
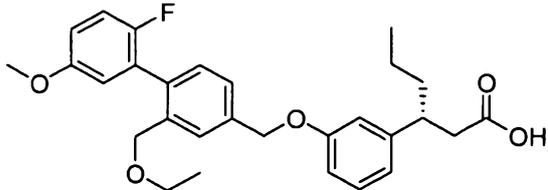
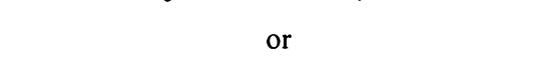
67.7	<p style="text-align: center;">or</p>	+++	++++
67.8	<p style="text-align: center;">or</p>	+++	++++
67.9		++	ND

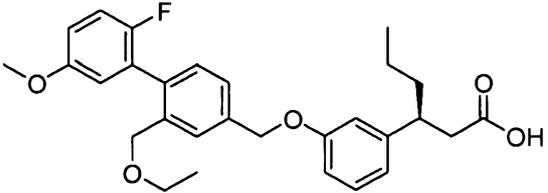
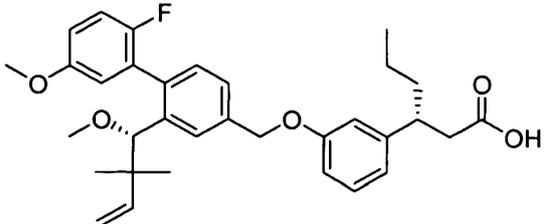
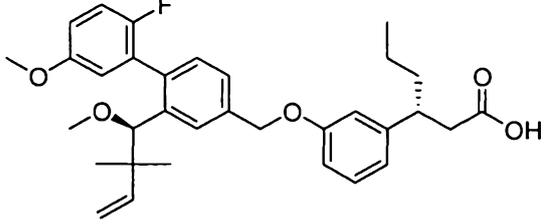
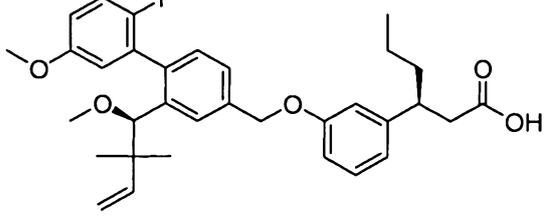
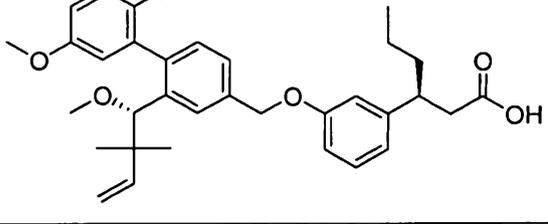
	<p>or</p> 		
67.10	<p>or</p> 	+++	ND
67.11	<p>or</p> 	+++	++++

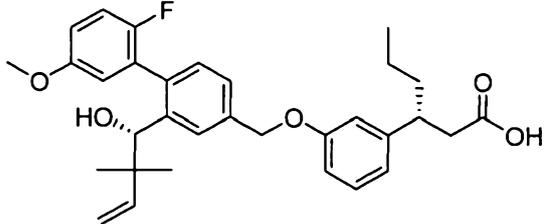
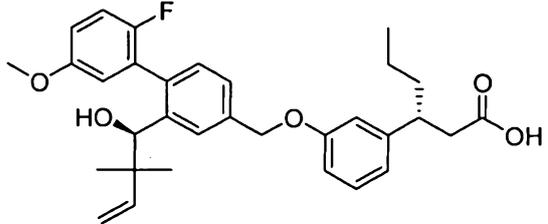
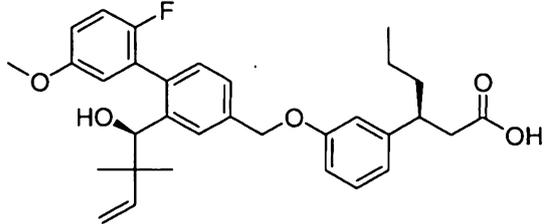
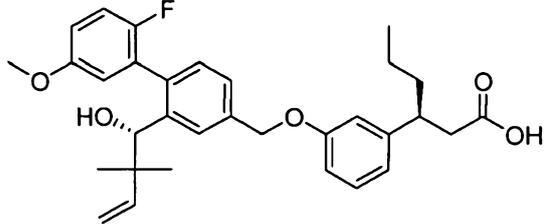
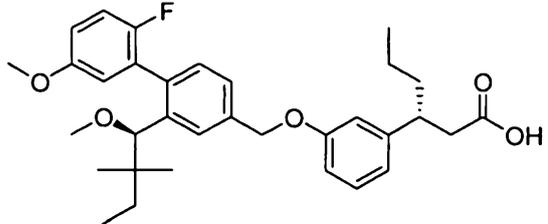
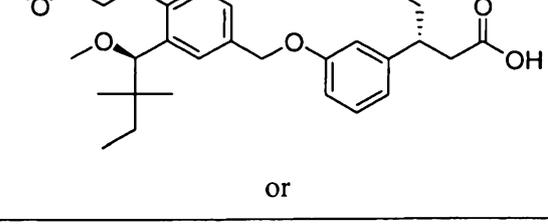
<p>67.12</p>	 <p>or</p>	<p>+++</p>	<p>++++</p>
<p>67.13</p>	 <p>or</p>	<p>+++</p>	<p>ND</p>
<p>67.14</p>	 <p>or</p>	<p>+++</p>	<p>ND</p>

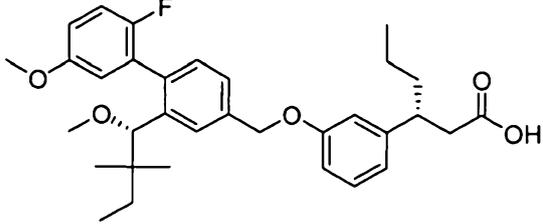
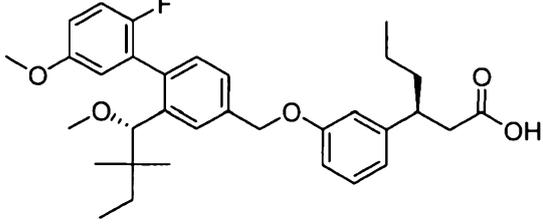
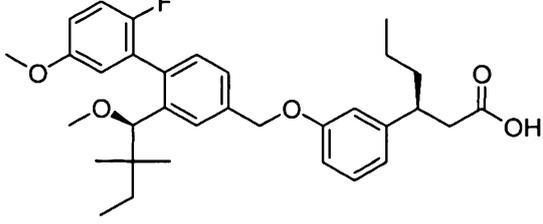
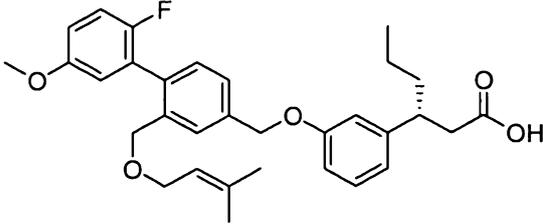
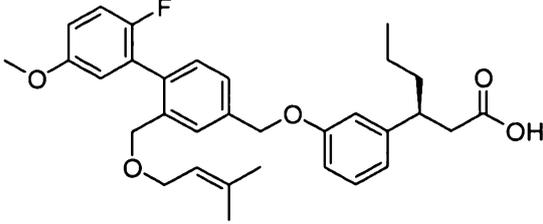
67.15	 or 	+++	ND
67.16	 or 	+++	ND
67.17		+++	ND

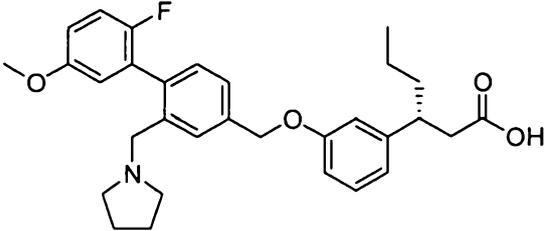
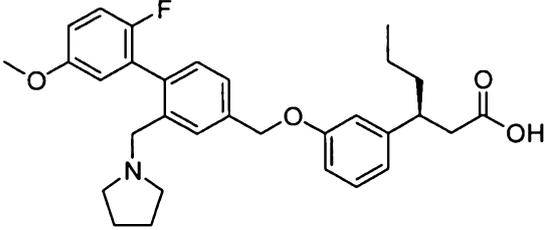
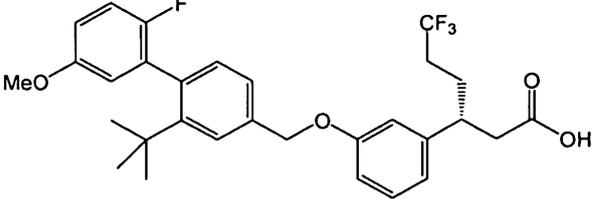
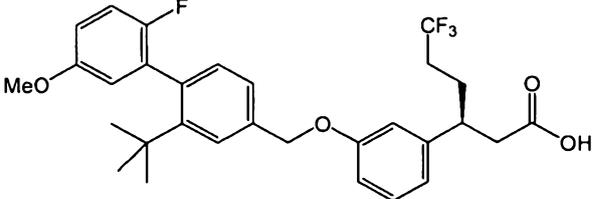
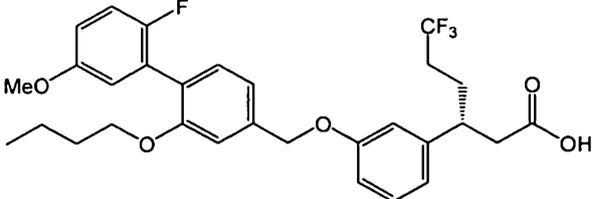
	<p>or</p> 		
67.18	 <p>or</p> 	++	ND
67.19	 <p>or</p> 	++	ND
67.20	 <p>or</p> 	+++	++++

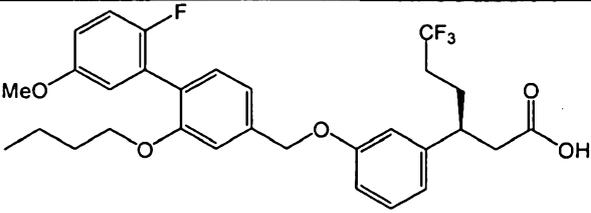
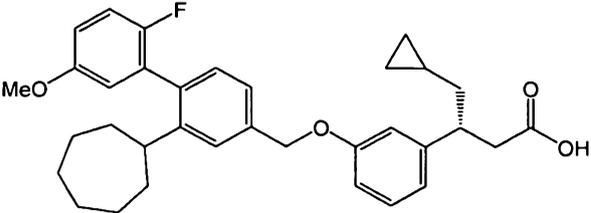
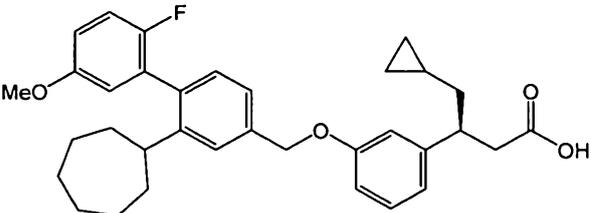
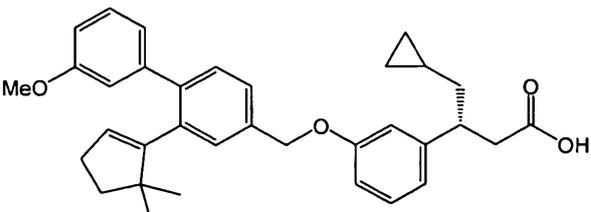
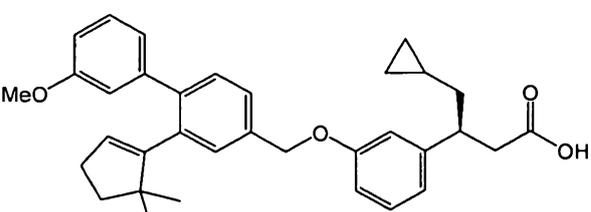
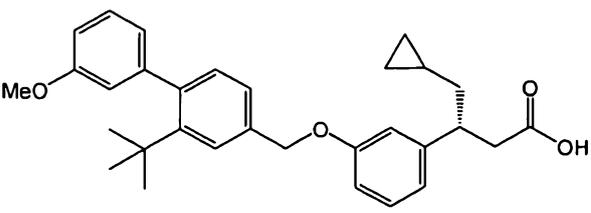
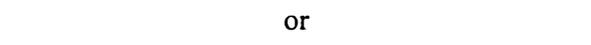
			
67.21	 or 	+++	++++
67.22	 or 	++	ND
67.23	 or 	++	ND

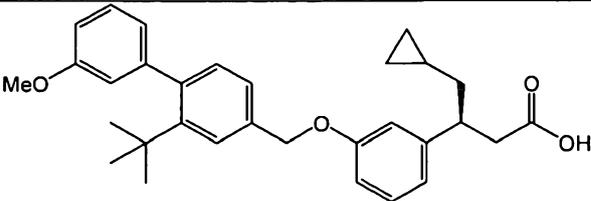
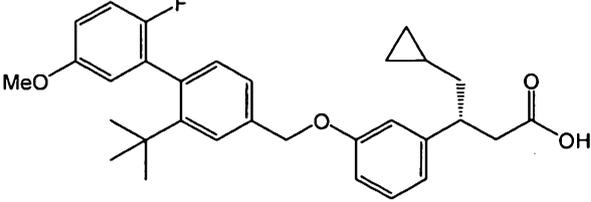
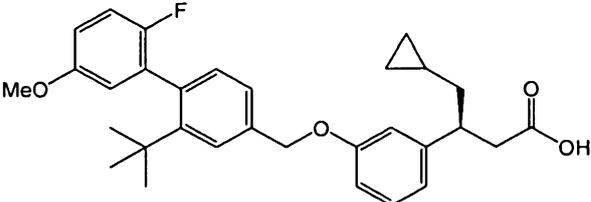
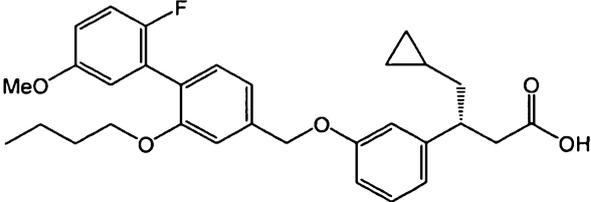
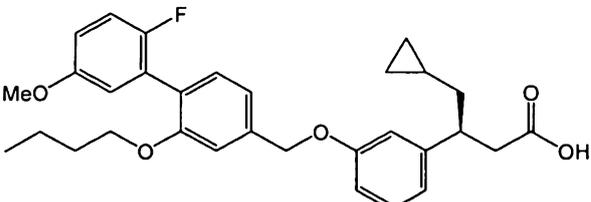
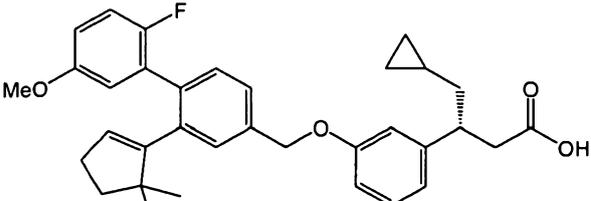
			
<p>67.24</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>+++</p>	<p>++++</p>

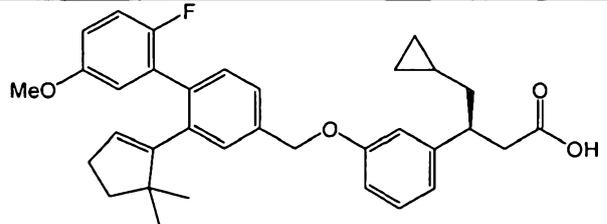
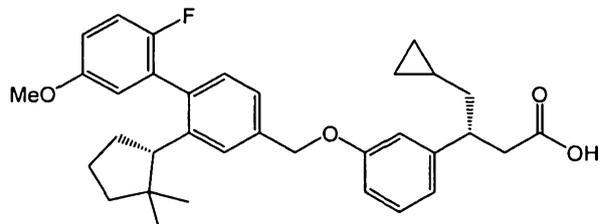
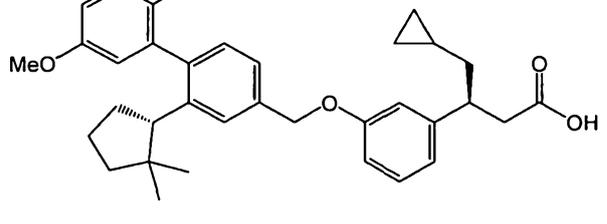
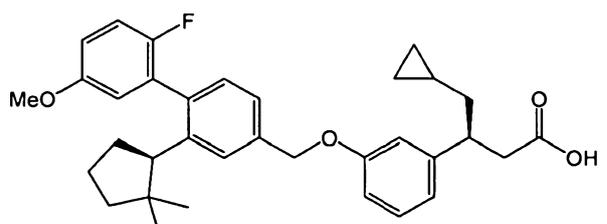
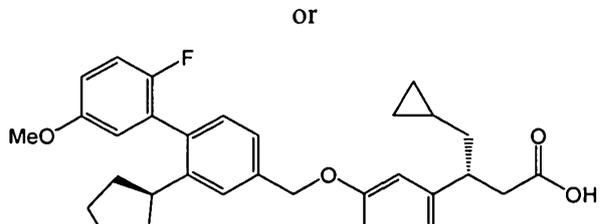
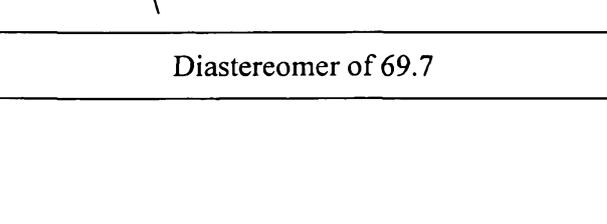
<p>67.25</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>++</p>	<p>ND</p>
<p>67.26</p>	 <p>or</p> 	<p>++</p>	<p>ND</p>

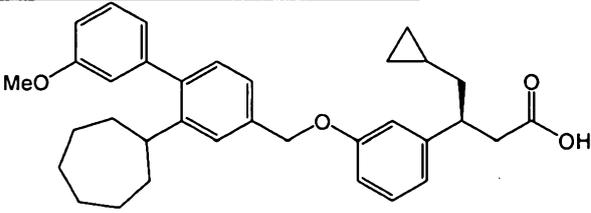
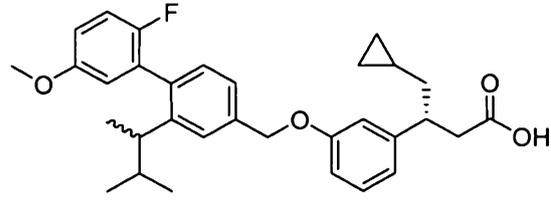
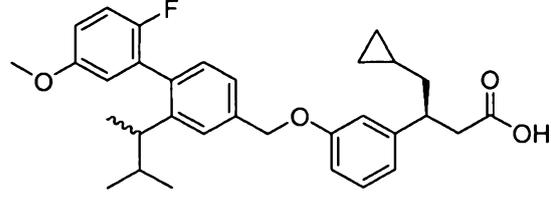
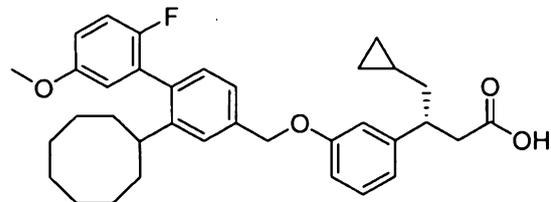
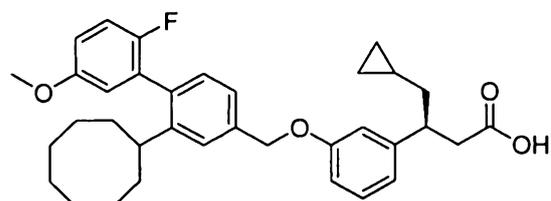
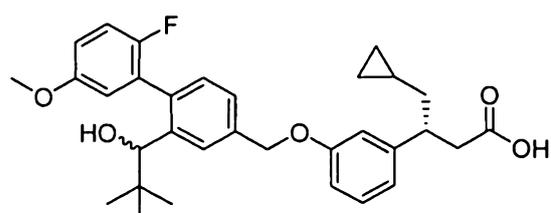
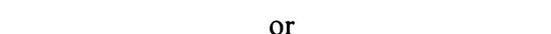
	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 		
<p>67.27</p>	 <p style="text-align: center;">or</p> 	<p style="text-align: center;">++</p>	<p style="text-align: center;">ND</p>

<p>67.28</p>	 <p>or</p> 	<p>++</p>	<p>ND</p>
<p>68.1</p>	 <p>or</p> 	<p>+++</p>	<p>ND</p>
<p>68.2</p>	 <p>or</p> 	<p>++</p>	<p>ND</p>

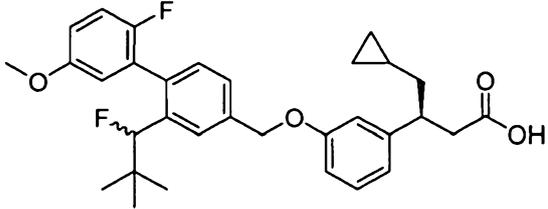
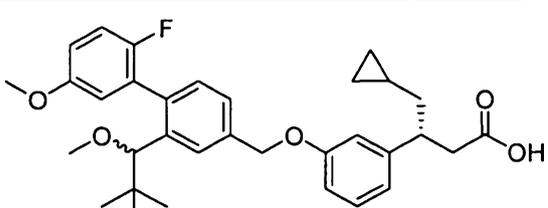
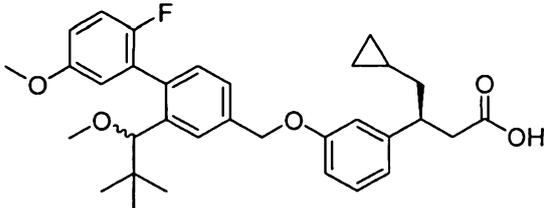
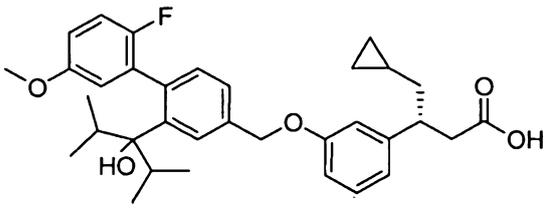
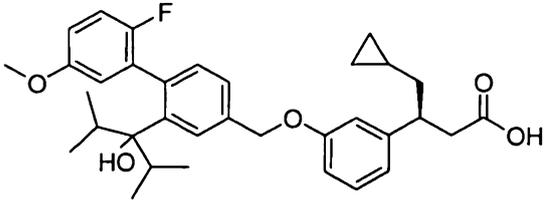
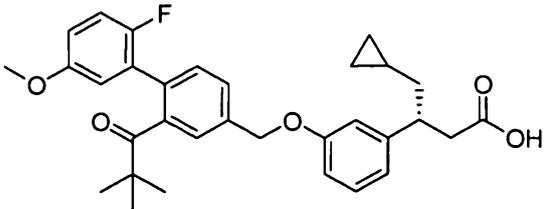
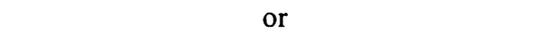
			
69.1	 <p style="text-align: center;">or</p> 	+++	+++++
69.2	 <p style="text-align: center;">or</p> 	+++	++++
69.3	 <p style="text-align: center;">or</p> 	+++	++++

			
69.4	 or 	+++	++++
69.5	 or 	+++	ND
69.6	 or 	+++	++++

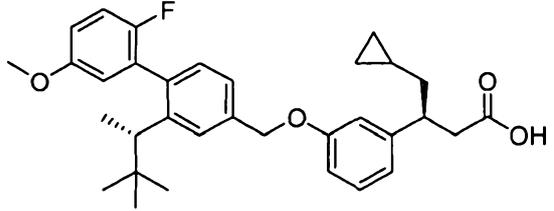
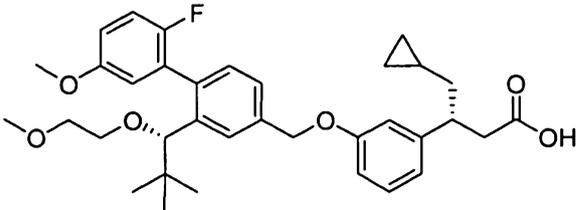
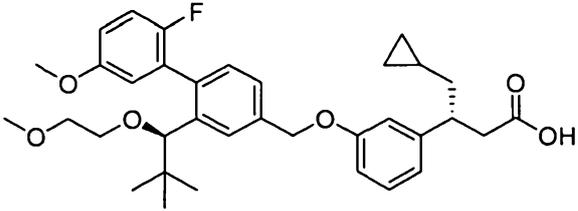
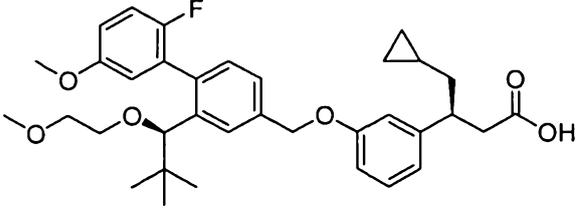
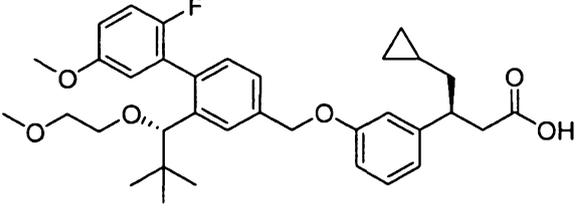
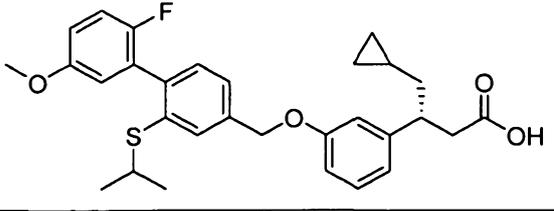
			
69.7		or	
			
			
			
69.8	Diastereomer of 69.7	++++	+++++

			
69.12	 <p style="text-align: center;">or</p> 	+++	+++++
69.13	 <p style="text-align: center;">or</p> 	+++	+++++
69.14	 <p style="text-align: center;">or</p> 	+++	+++

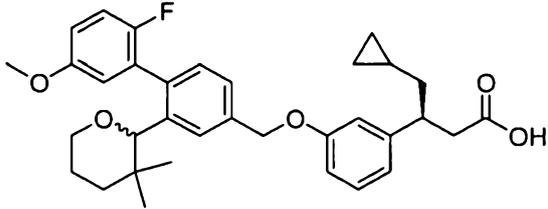
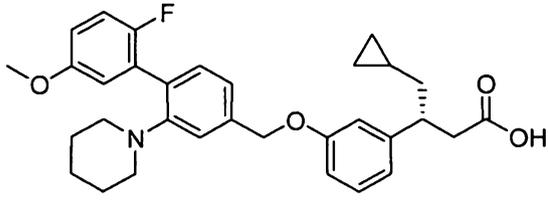
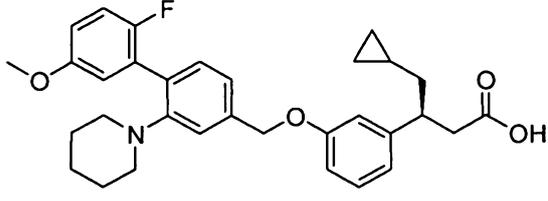
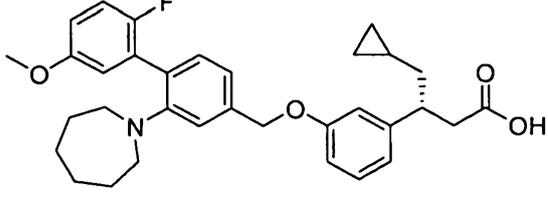
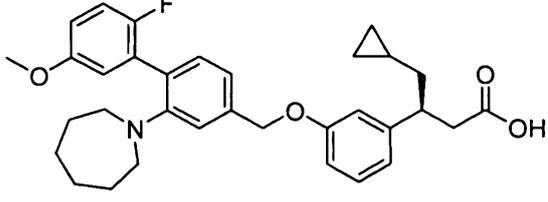
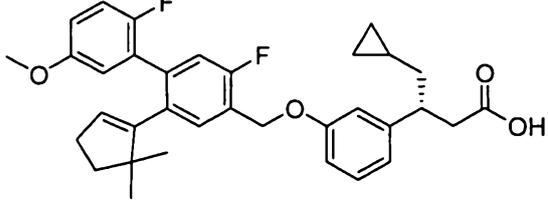
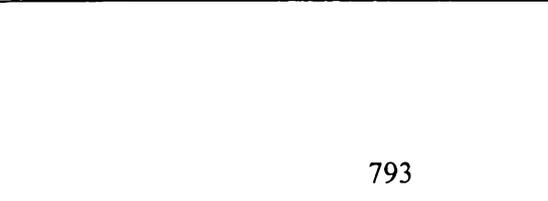
69.15	<p style="text-align: center;">or</p>	+++	++++
69.16	<p style="text-align: center;">or</p>	++++	++++
69.17	<p style="text-align: center;">or</p>	+++	+++++

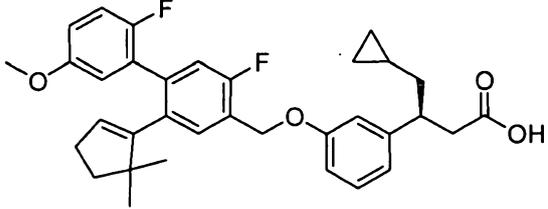
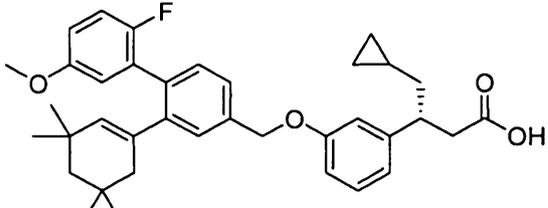
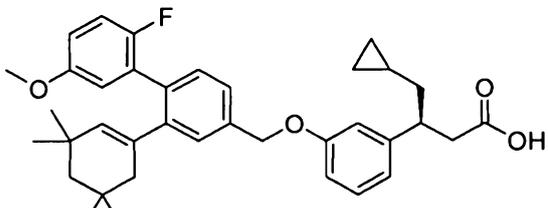
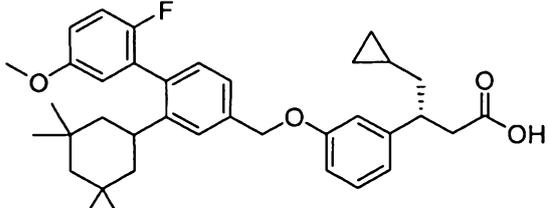
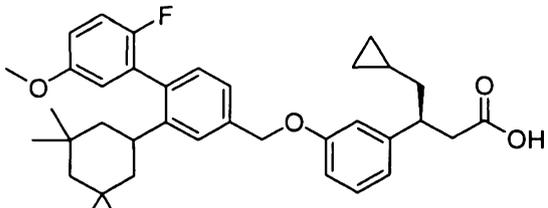
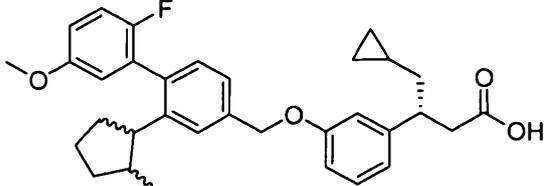
			
69.18	 or 	+++	+++++
69.19	 or 	+++	+++
69.20	 or 	++	ND

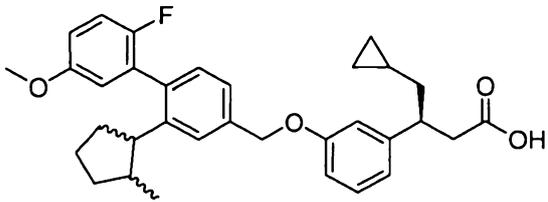
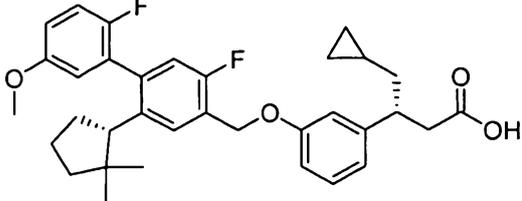
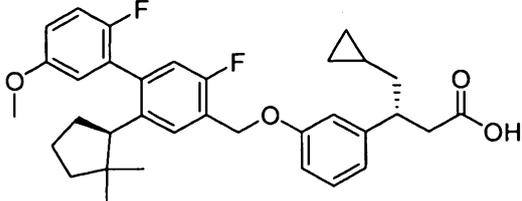
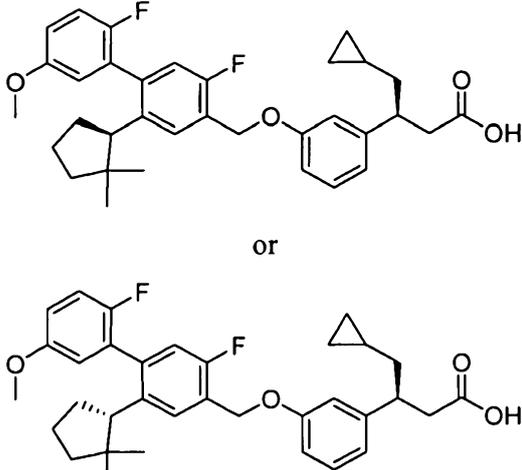
<p>69.21</p>	<p>or</p>	<p>+++</p>	<p>++++</p>
<p>69.22</p>	<p>or</p> <p>or</p> <p>or</p>	<p>+++</p>	<p>+++++</p>

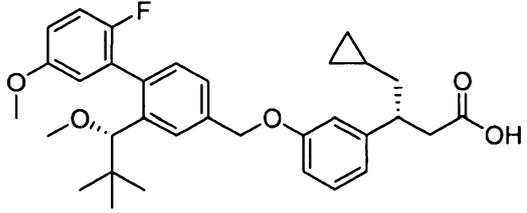
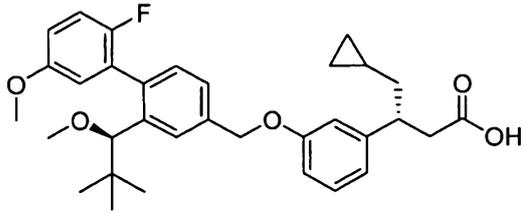
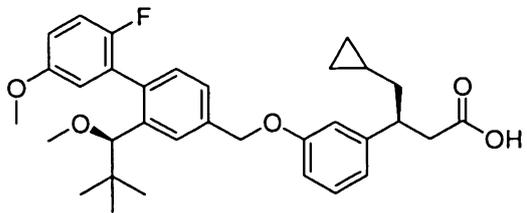
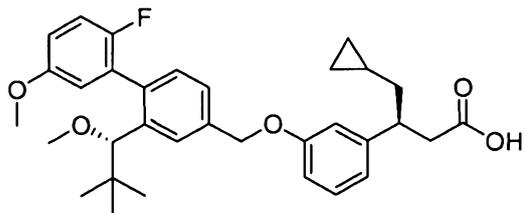
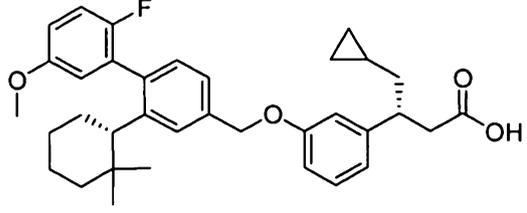
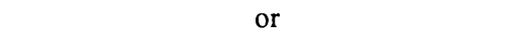
			
69.23	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	++++	+++++
69.24		+++	++++

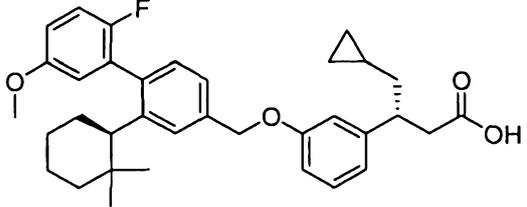
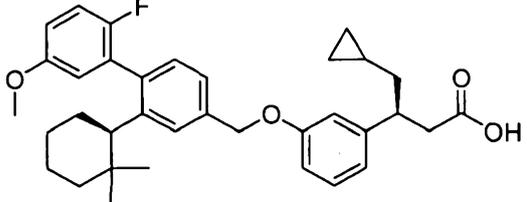
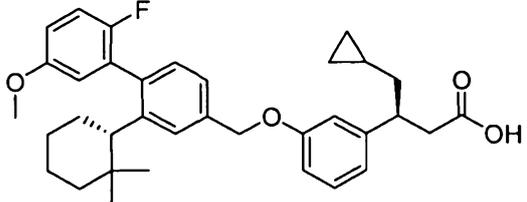
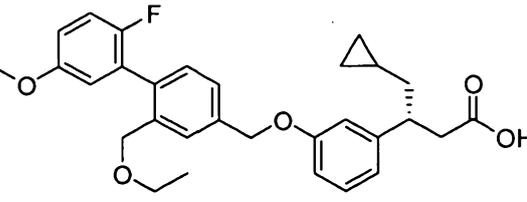
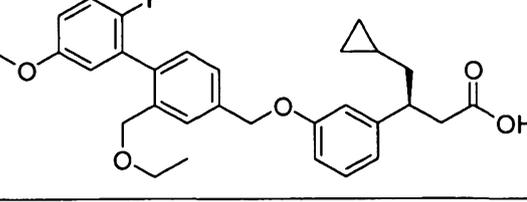
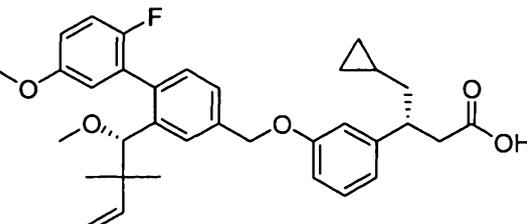
	<p>or</p>		
69.25	<p>or</p>	++	ND
69.26	<p>or</p>	++	ND
69.27	<p>or</p>	+++	ND

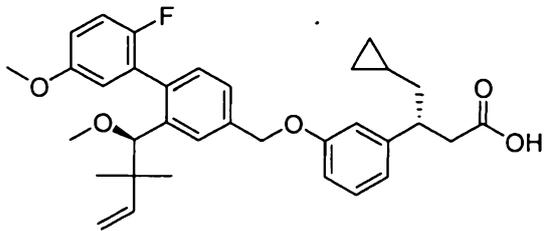
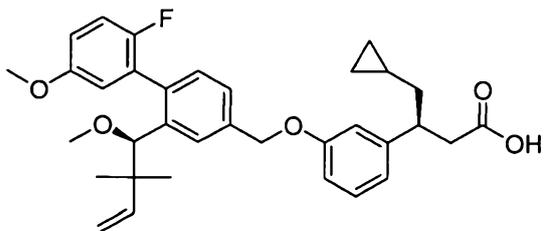
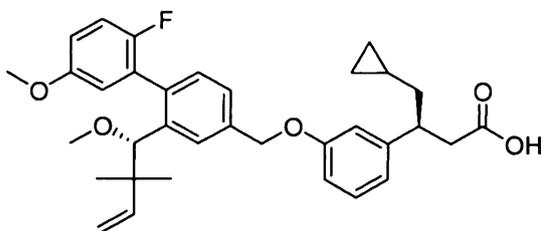
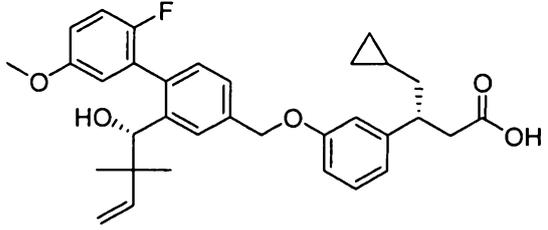
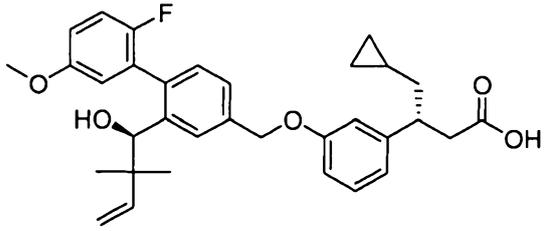
			
69.28	 <p style="text-align: center;">or</p> 	+++	++++
69.29	 <p style="text-align: center;">or</p> 	+++	+++
69.30	 <p style="text-align: center;">or</p> 	+++	+++++

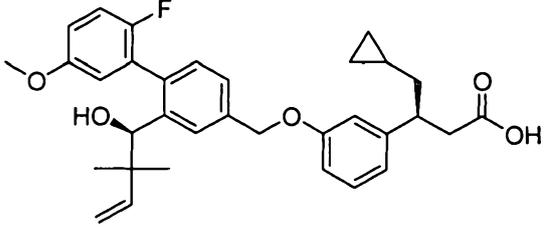
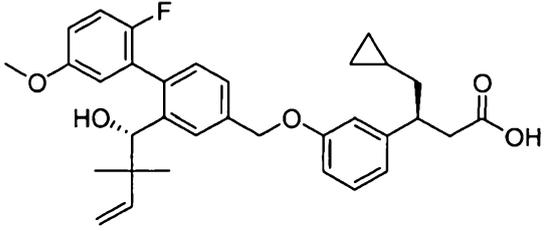
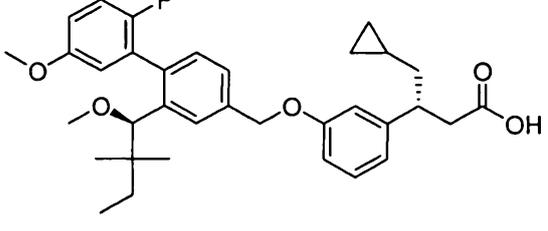
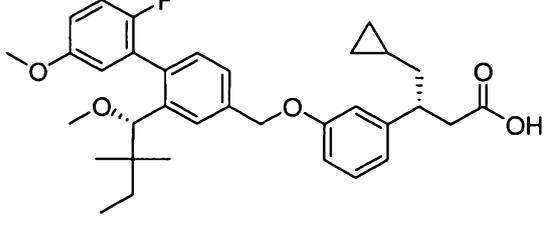
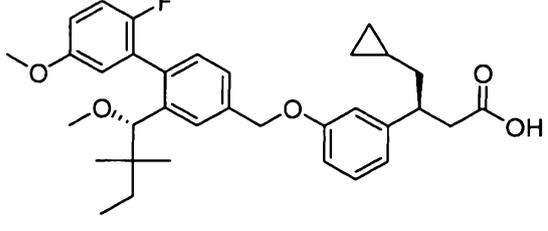
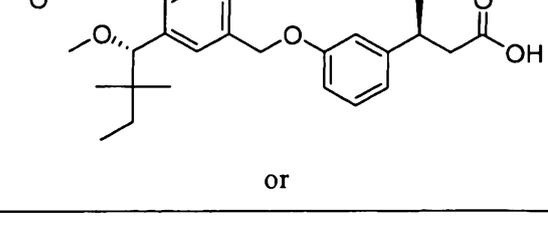
			
69.31	 <p style="text-align: center;">or</p> 	+++	++++
69.32	 <p style="text-align: center;">or</p> 	+++	++++
69.33		+++	++++

	<p style="text-align: center;">or</p> 		
<p>69.34</p>			
	<p style="text-align: center;">or</p>		
			
	<p style="text-align: center;">or</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">+++++</p>
			

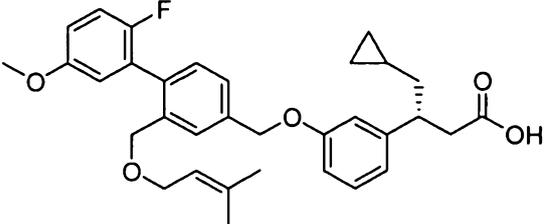
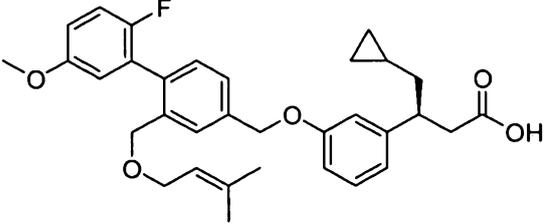
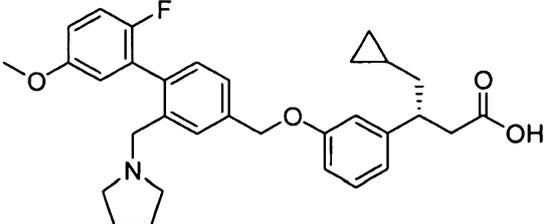
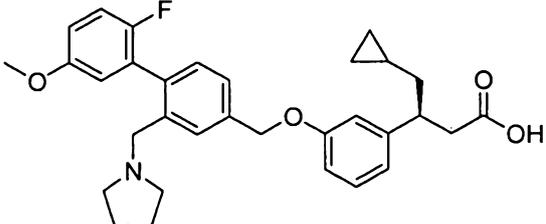
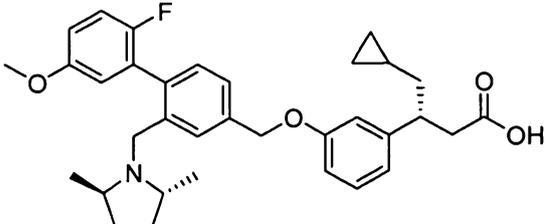
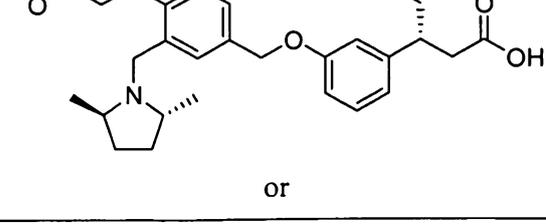
<p>69.35</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>++++</p>	<p>+++++</p>
<p>69.36</p>	 <p>or</p> 	<p>+++</p>	<p>+++++</p>

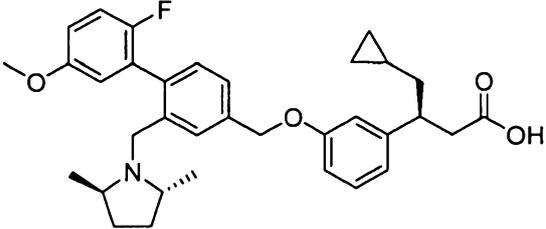
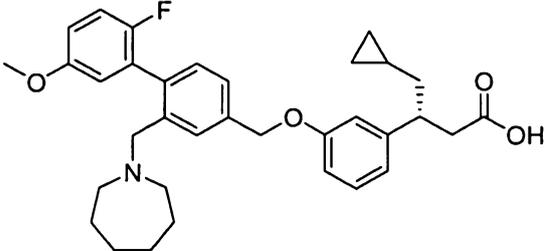
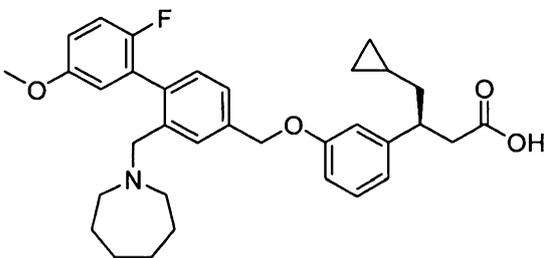
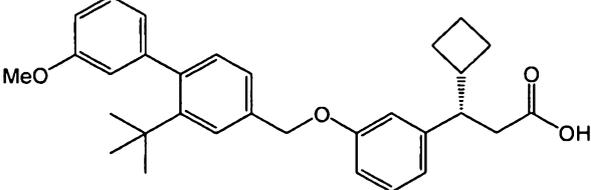
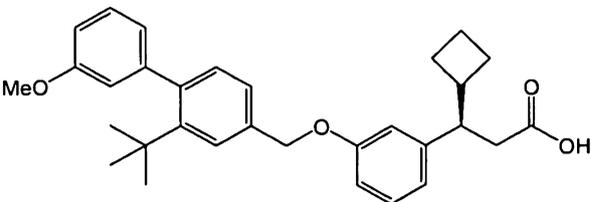
	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 		
<p>69.37</p>	 <p style="text-align: center;">or</p> 	<p style="text-align: center;">++</p>	<p style="text-align: center;">ND</p>
<p>69.38</p>		<p style="text-align: center;">+++</p>	<p style="text-align: center;">+++++</p>

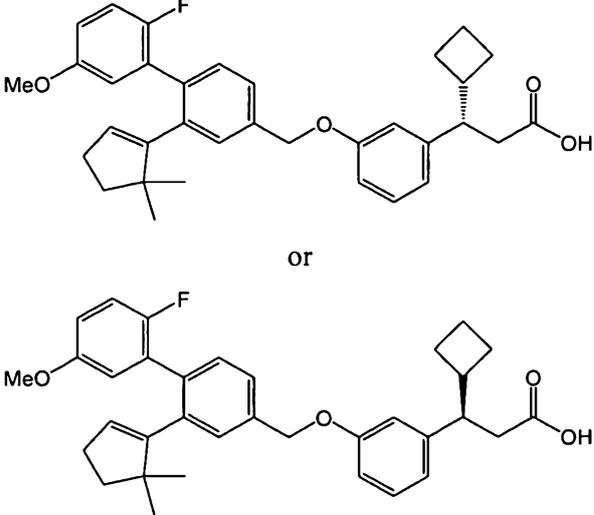
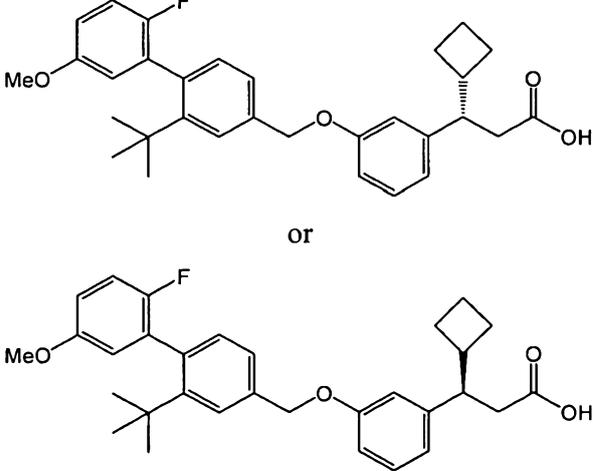
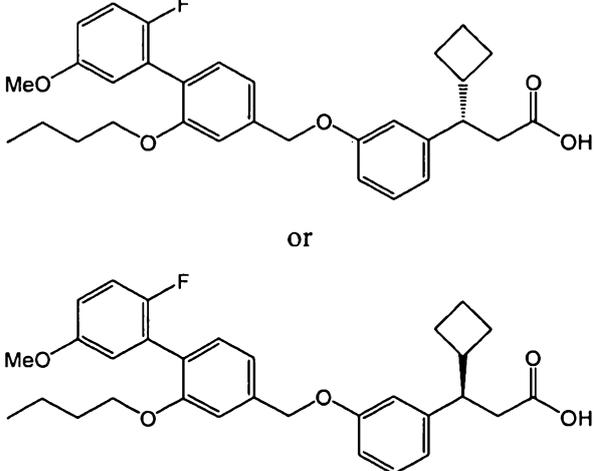
	<p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 		
<p>69.39</p>	<p style="text-align: center;">Diastereomer of 69.38</p>	<p style="text-align: center;">++</p>	<p style="text-align: center;">ND</p>
<p>69.40</p>	<p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>	<p style="text-align: center;">++</p>	<p style="text-align: center;">ND</p>

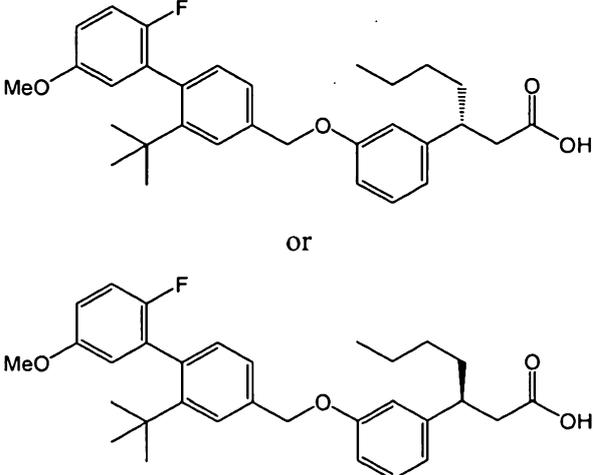
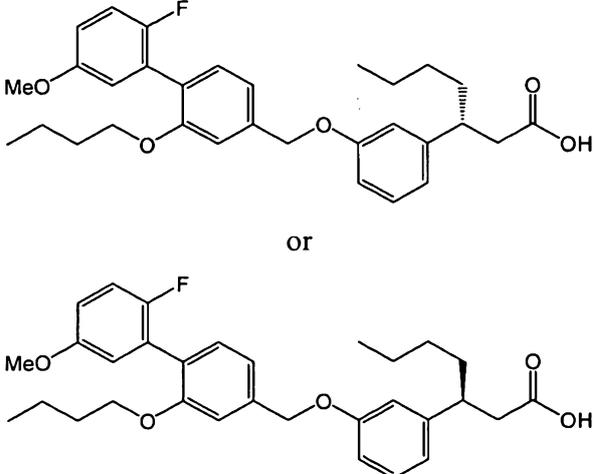
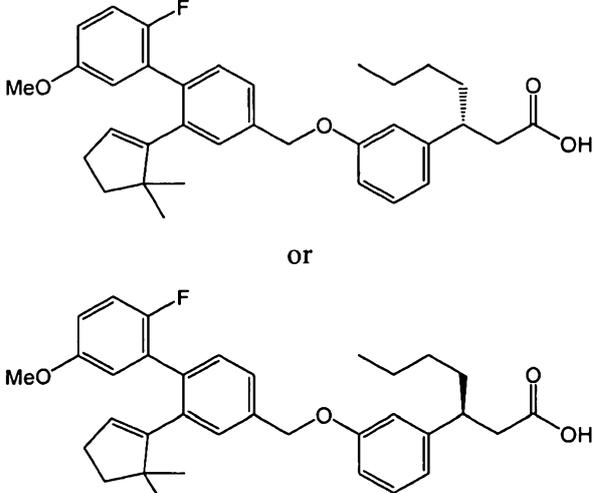
	 <p style="text-align: center;">or</p> 		
<p>69.41</p>	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	<p style="text-align: center;">+++</p>	<p style="text-align: center;">ND</p>

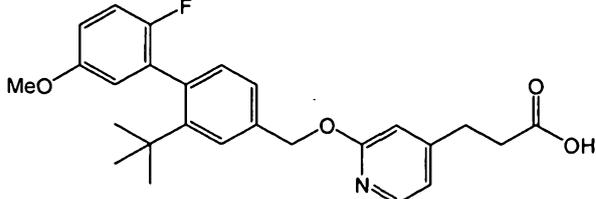
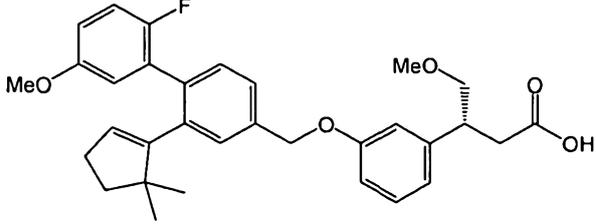
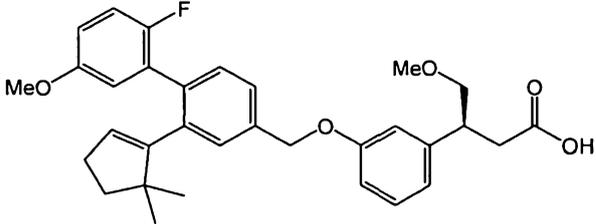
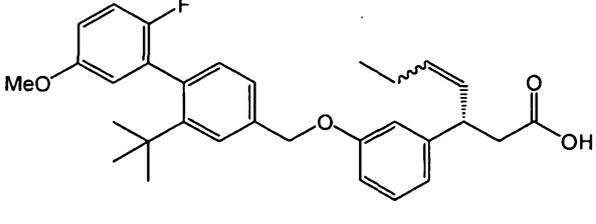
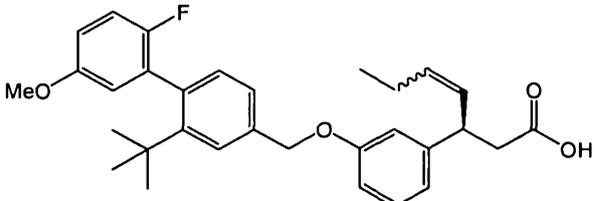
69.42	Diastereomer of 69.41	+++	++++
69.43		++	ND
69.44	Diastereomer of 69.43	+++	++++

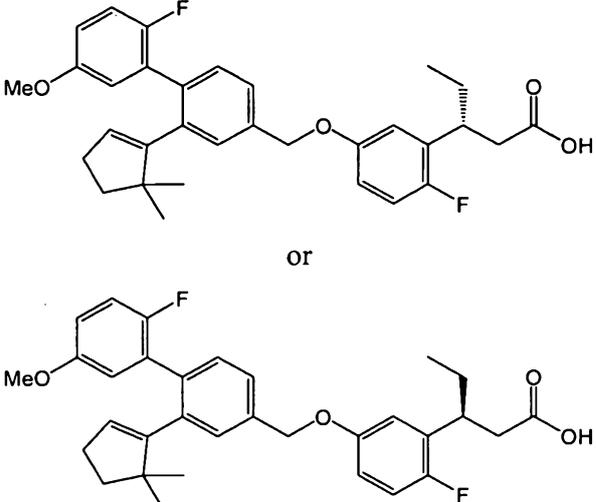
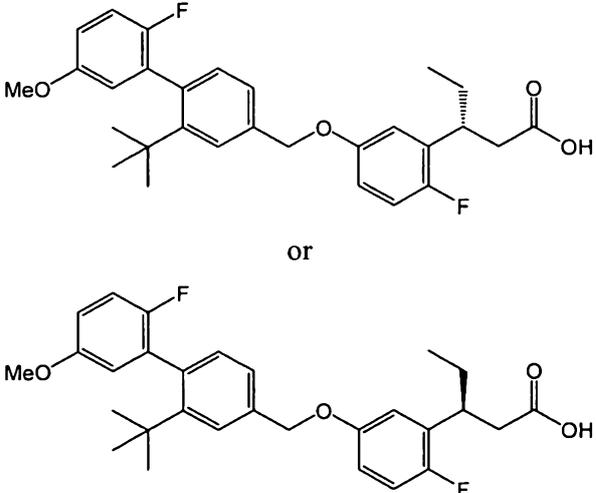
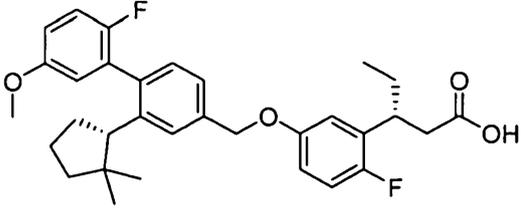
<p>69.45</p>	 <p>or</p> 	<p>++</p>	<p>ND</p>
<p>69.46</p>	 <p>or</p> 	<p>++</p>	<p>ND</p>
<p>69.47</p>	 <p>or</p> 	<p>+++</p>	<p>ND</p>

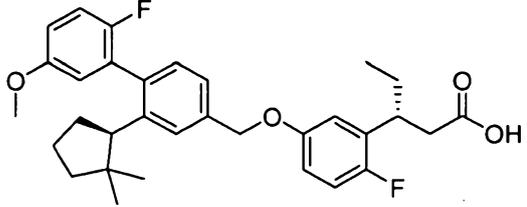
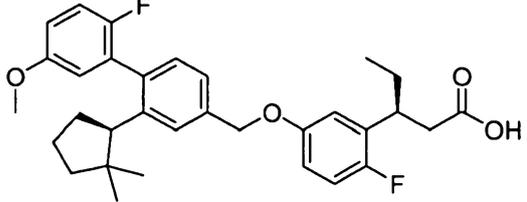
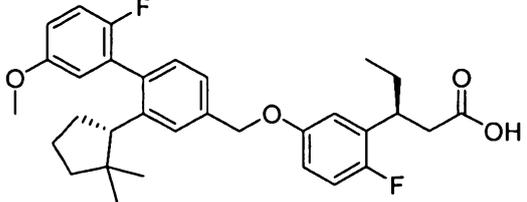
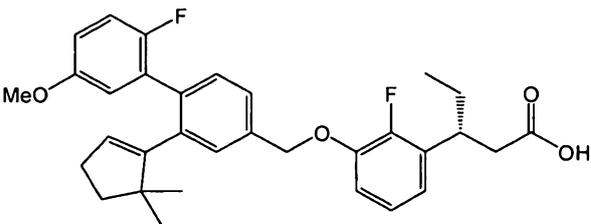
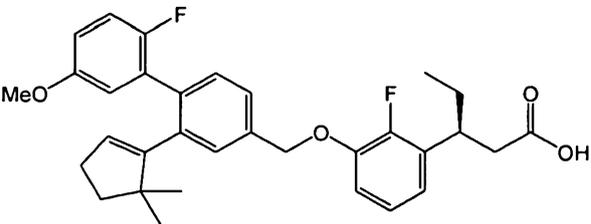
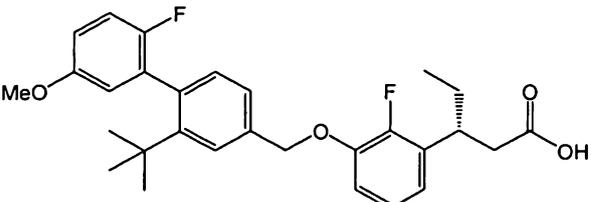
			
69.48	 or 	++	ND
70.1	 or 	+++	++++

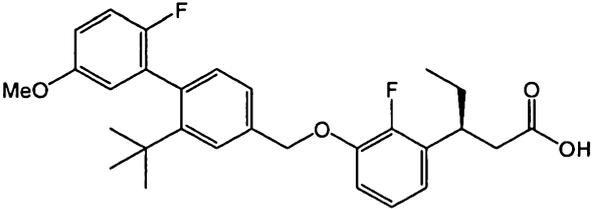
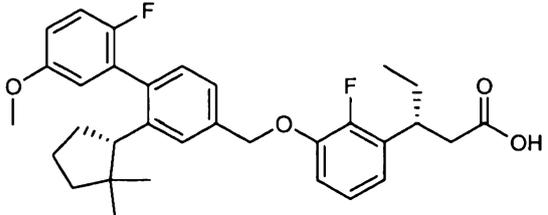
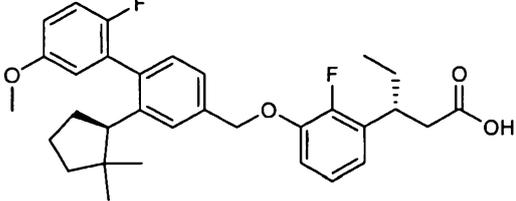
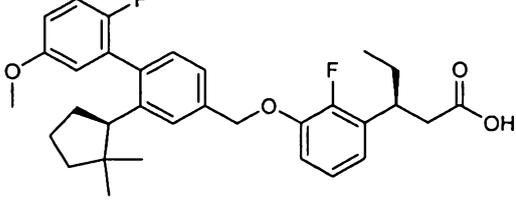
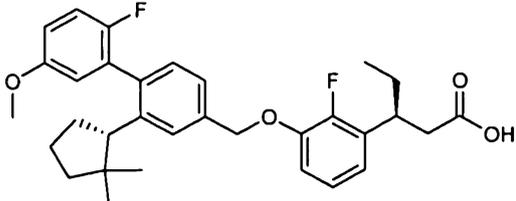
<p>70.2</p>	 <p>or</p>	<p>+++</p>	<p>++++</p>
<p>70.3</p>	 <p>or</p>	<p>+++</p>	<p>++++</p>
<p>70.4</p>	 <p>or</p>	<p>+++</p>	<p>+++</p>

<p>71.1</p>	 <p>or</p>	<p>+++</p>	<p>ND</p>
<p>71.2</p>	 <p>or</p>	<p>+++</p>	<p>+++</p>
<p>71.3</p>	 <p>or</p>	<p>+++</p>	<p>++++</p>

72		+++	++
73	Enantiomer of 51	++	ND
74	 <p style="text-align: center;">or</p> 	++	ND
75	 <p style="text-align: center;">or</p> 	+++	ND

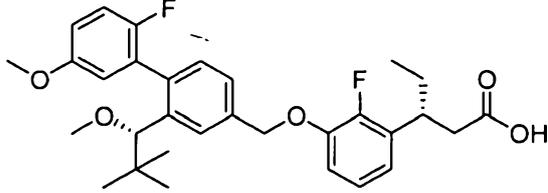
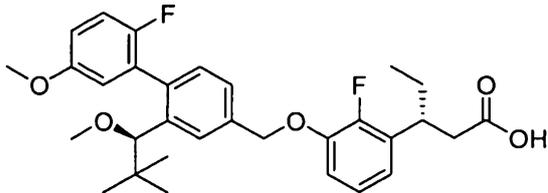
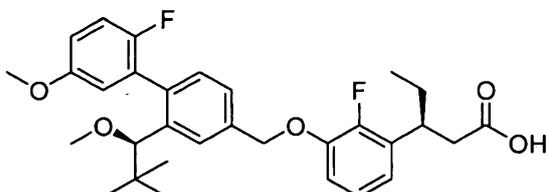
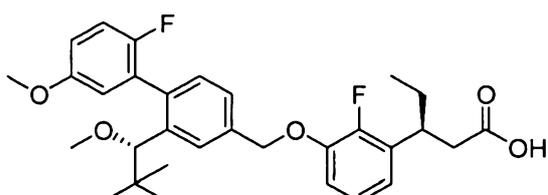
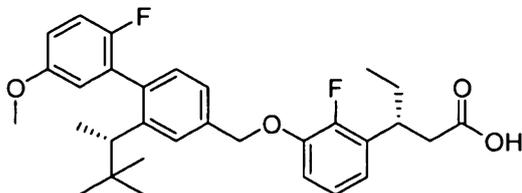
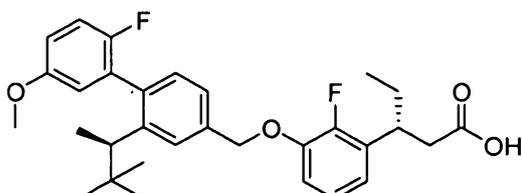
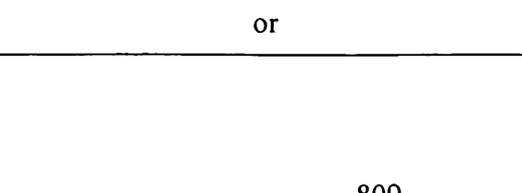
<p>76.1</p>	 <p>or</p>	<p>+++</p>	<p>++++</p>
<p>76.2</p>	 <p>or</p>	<p>++</p>	<p>ND</p>
<p>76.3</p>	 <p>or</p>	<p>+++</p>	<p>++++</p>

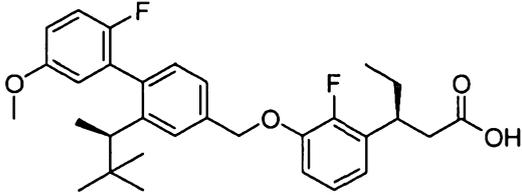
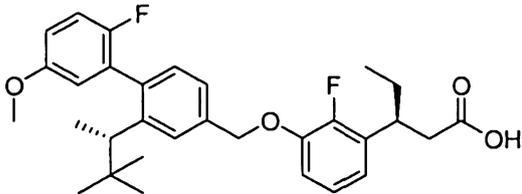
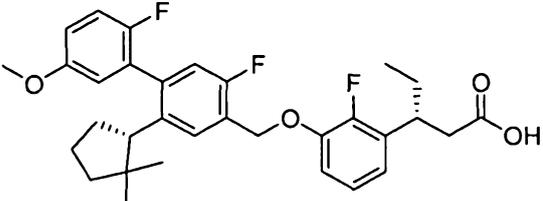
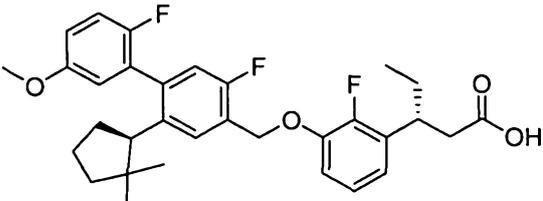
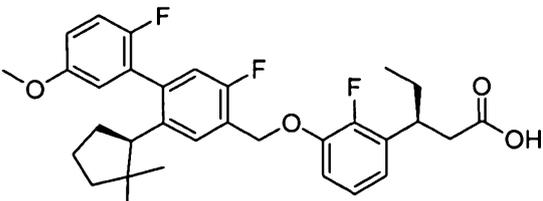
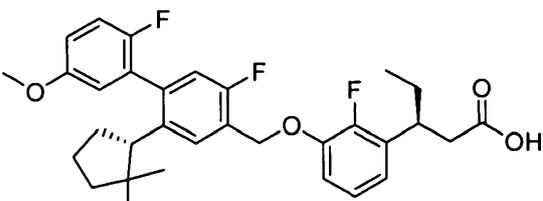
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<p>77.1</p>	 <p style="text-align: center;">or</p> 	<p style="text-align: center;">+++</p>	<p style="text-align: center;">++++</p>
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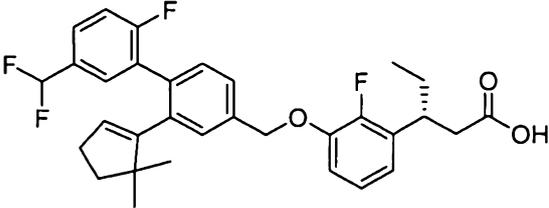
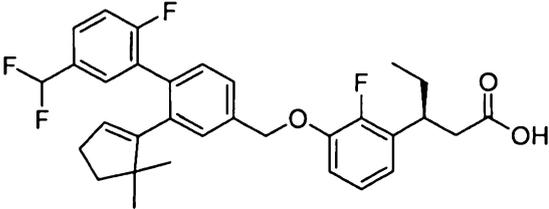
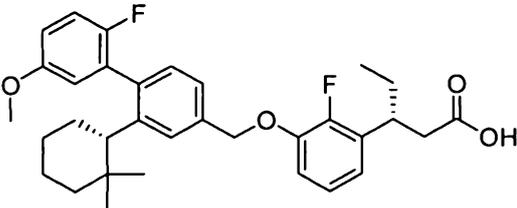
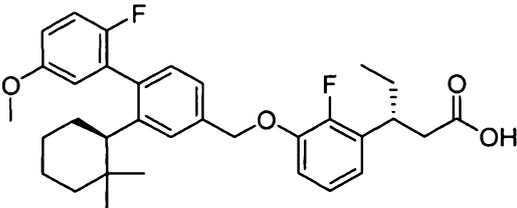
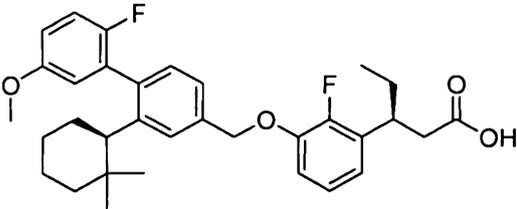
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	<p style="text-align: center;">or</p> 		

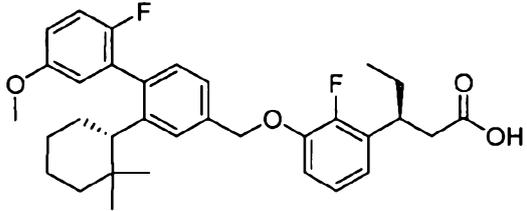
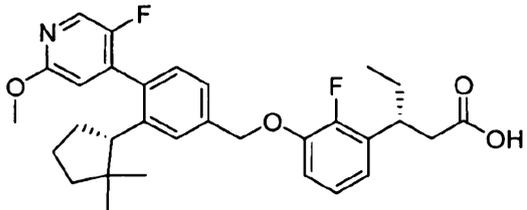
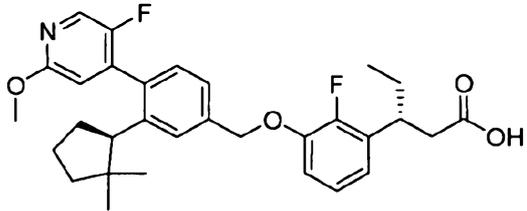
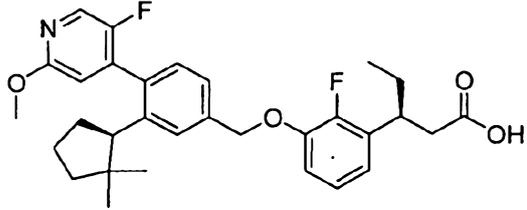
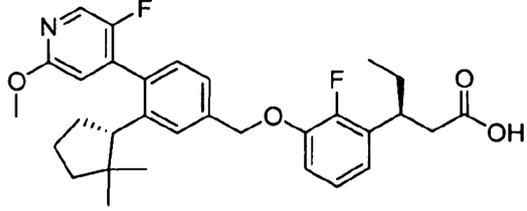
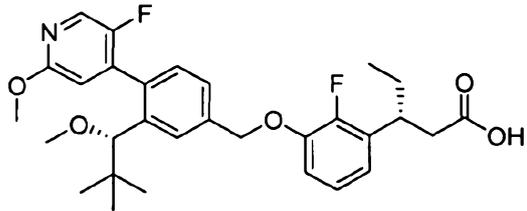
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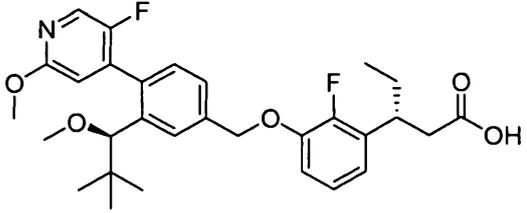
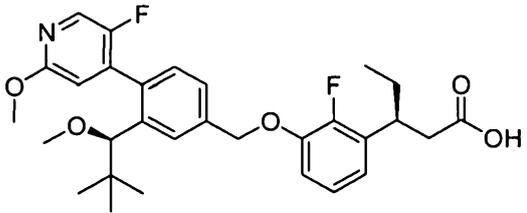
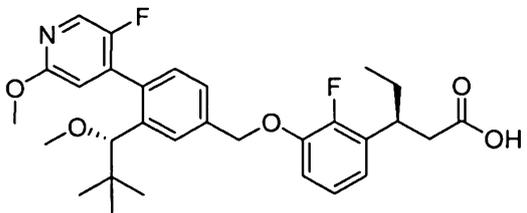
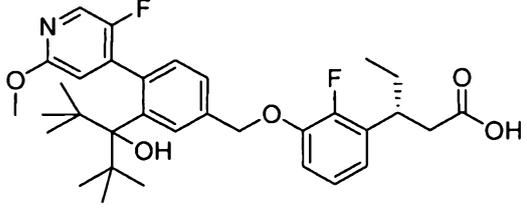
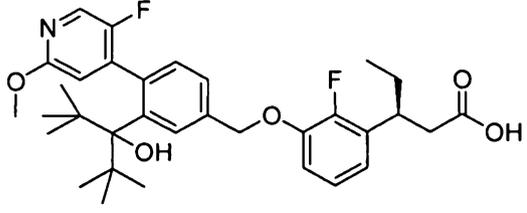
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<p>77.4</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>+++</p>	<p>+++++</p>
<p>77.5</p>	 <p>or</p>  <p>or</p> 	<p>+++</p>	<p>+++++</p>

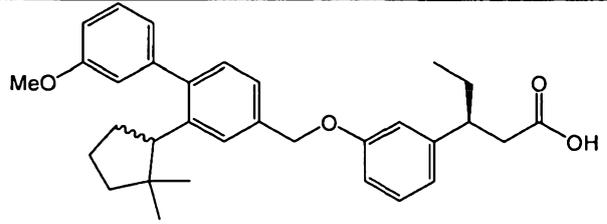
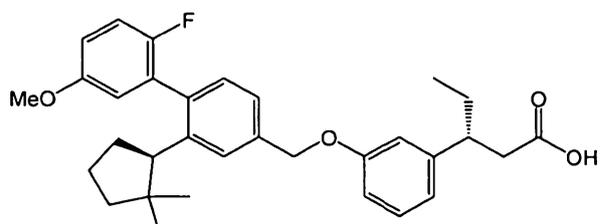
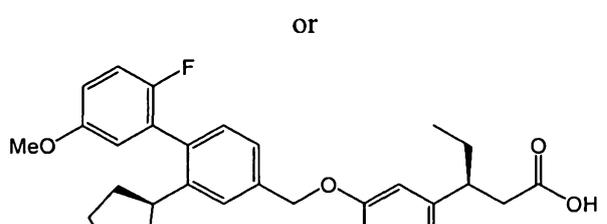
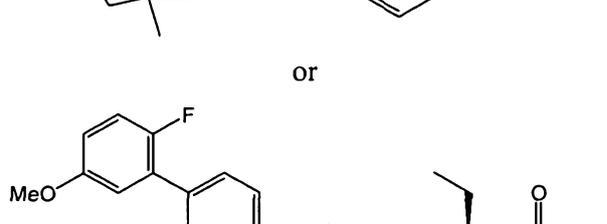
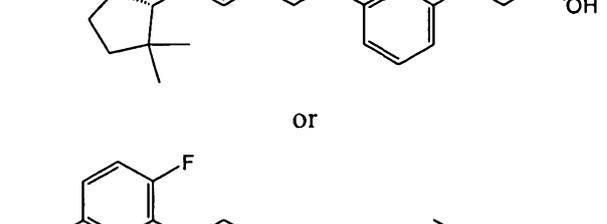
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<p>77.6</p>	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	<p style="text-align: center;">+++</p>	<p style="text-align: center;">+++++</p>

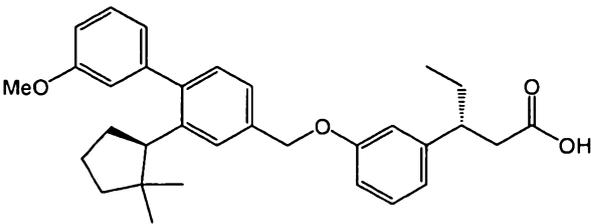
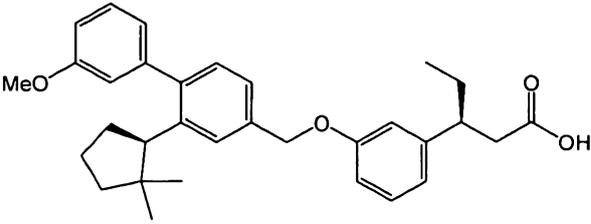
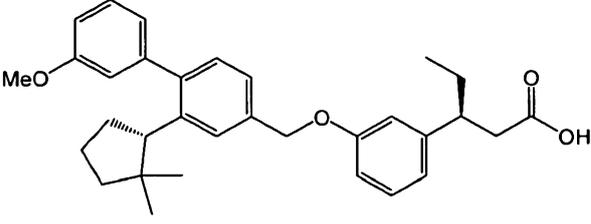
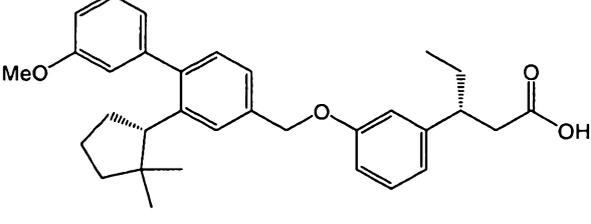
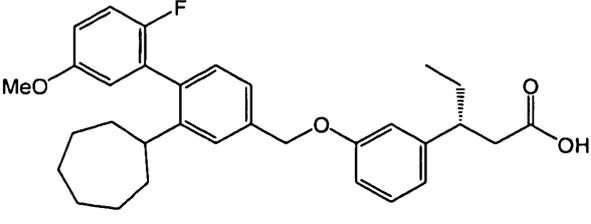
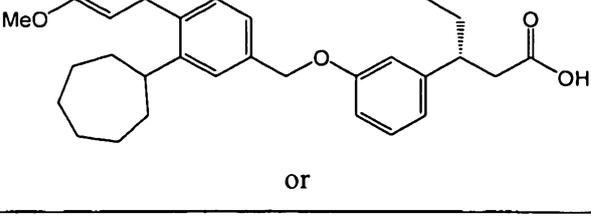
<p>77.7</p>	 <p>or</p> 	<p>++</p>	<p>+++</p>
<p>77.8</p>	 <p>or</p>  <p>or</p> 	<p>+++</p>	<p>+++++</p>

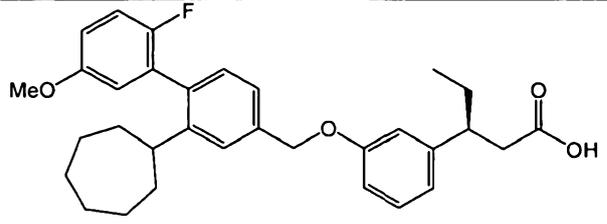
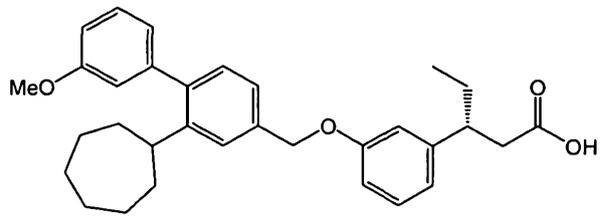
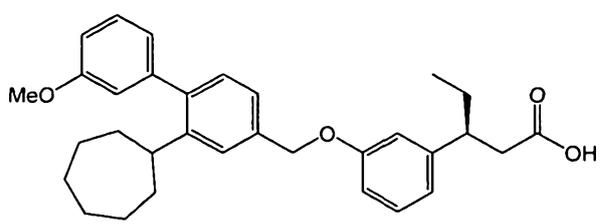
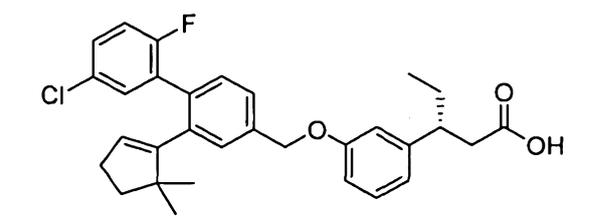
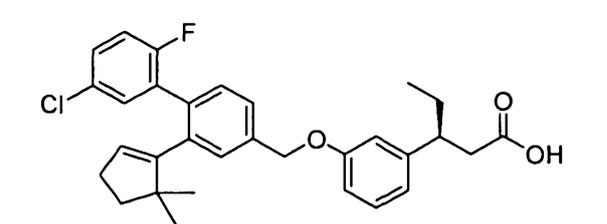
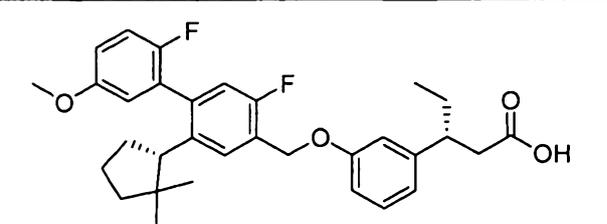
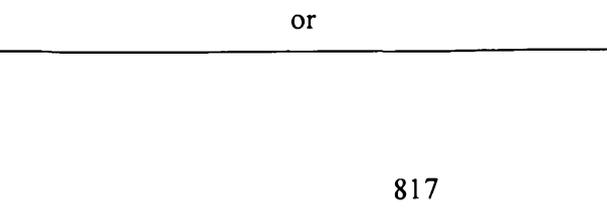
			
77.9	 or  or  or 	+++	+++++
77.10		+++	+++++

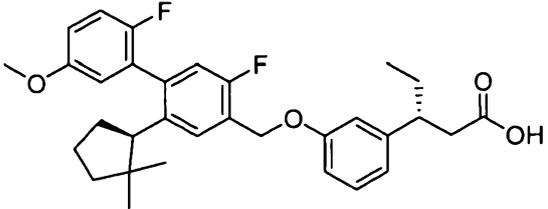
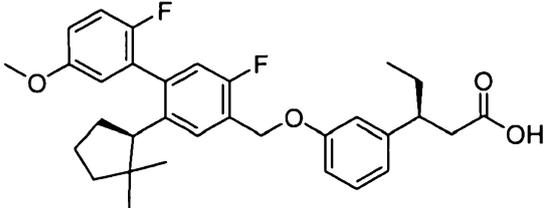
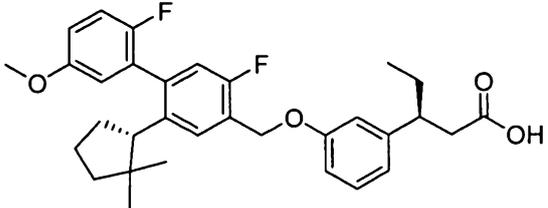
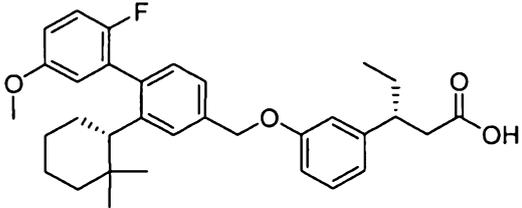
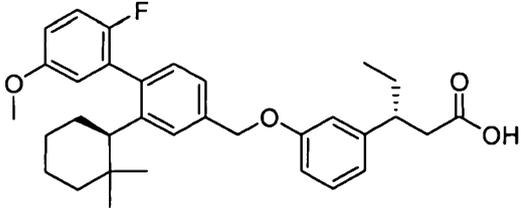
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<p>77.11</p>	<p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	<p style="text-align: center;">+++</p>	<p style="text-align: center;">+++++</p>

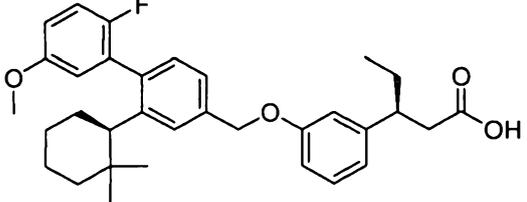
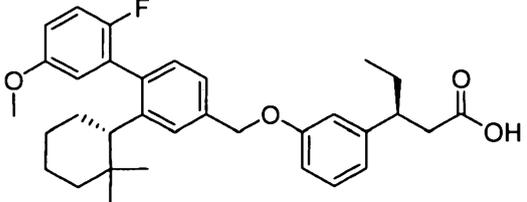
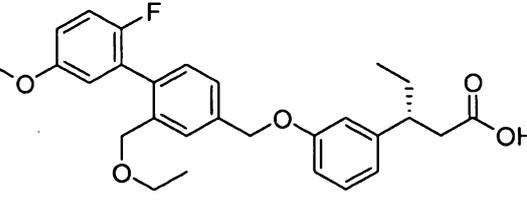
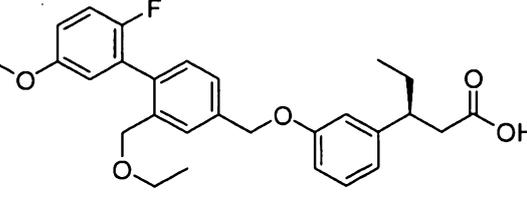
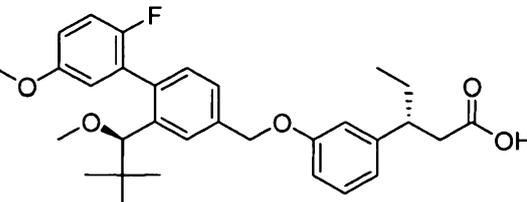
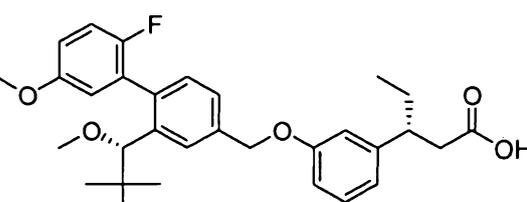
<p>77.12</p>	<p>or</p>	<p>++</p>	<p>ND</p>
<p>78.1</p>	<p>or</p>	<p>ND</p>	<p>ND</p>
<p>78.2</p>	<p>or</p>	<p>ND</p>	<p>ND</p>

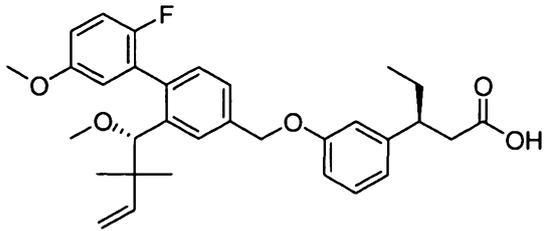
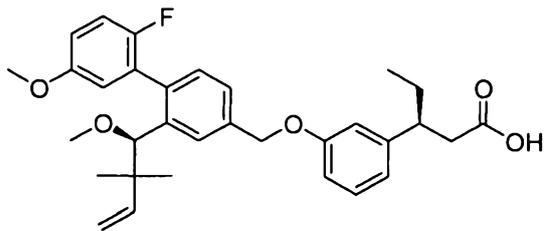
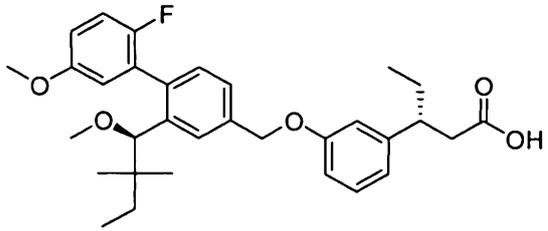
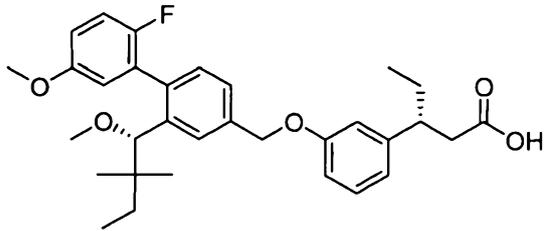
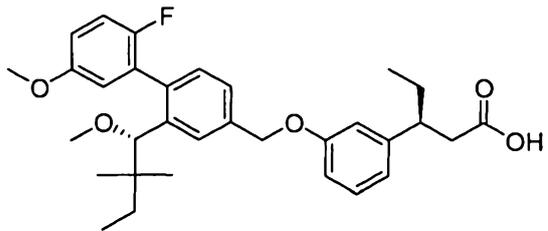
			
78.3	 <p>or</p>  <p>or</p>  <p>or</p> 	+++	ND
78.4	Diastereomer of 78.3	++++	+++++

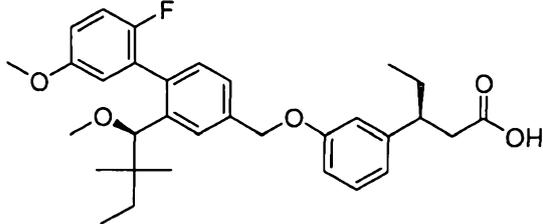
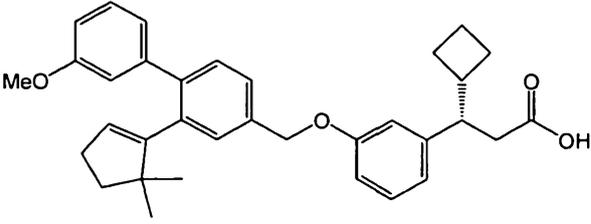
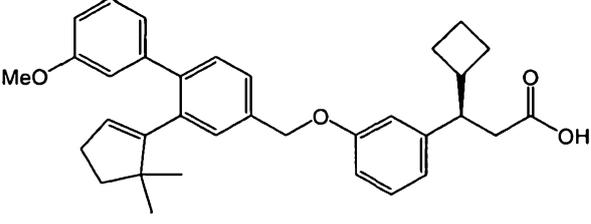
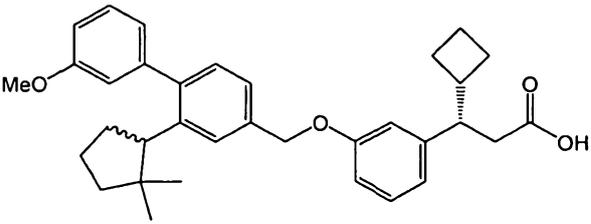
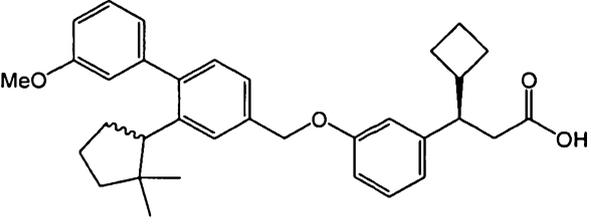
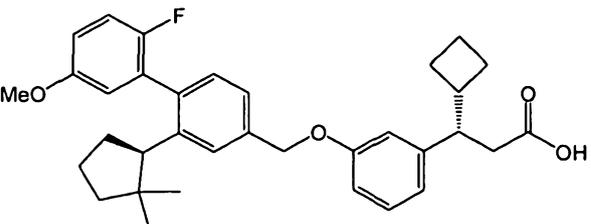
<p>78.5</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>+++</p>	<p>ND</p>
<p>78.6</p>	<p>Diastereomer of 78.5</p>	<p>++++</p>	<p>+++++</p>
<p>78.7</p>	 <p>or</p> 	<p>+++</p>	<p>++++</p>

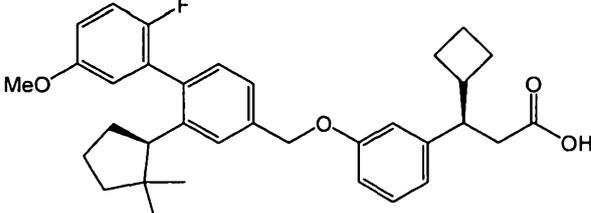
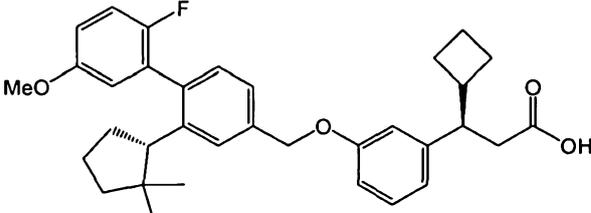
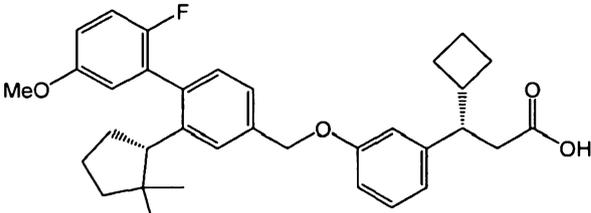
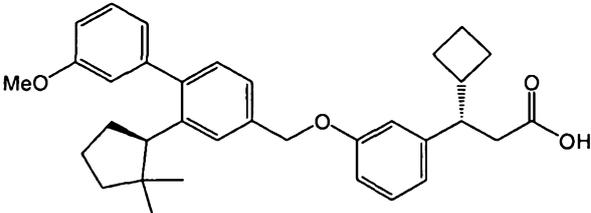
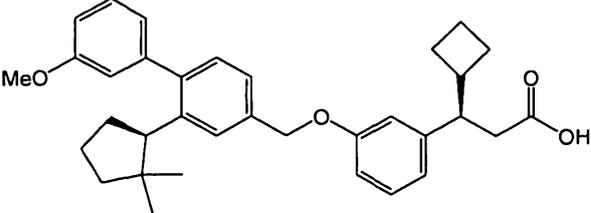
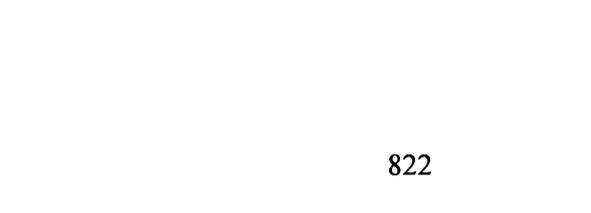
			
78.8	 or 	+++	++++
78.9	 or 	+++	++++
78.10	 or 	+++	+++++

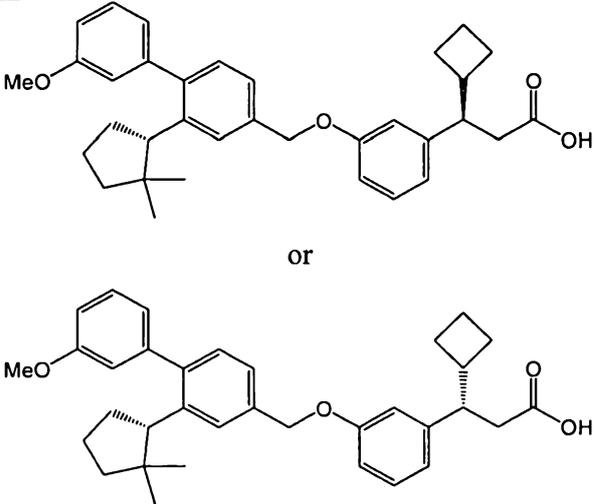
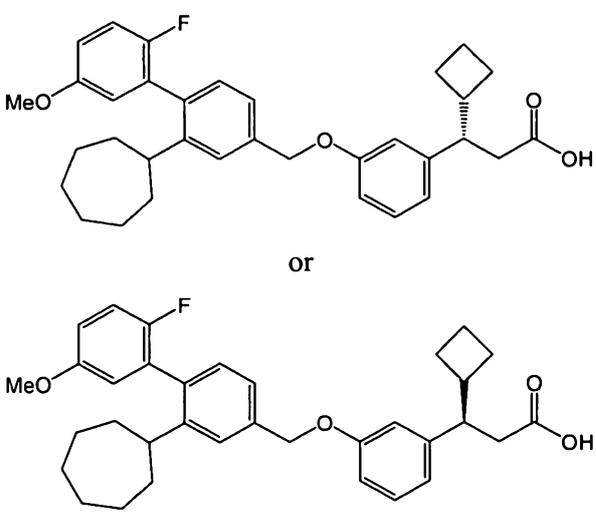
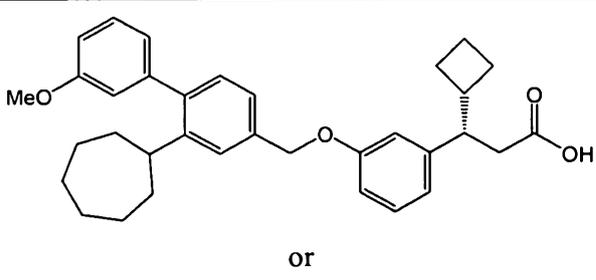
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<p>78.11</p>	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	<p style="text-align: center;">++++</p>	<p style="text-align: center;">+++++</p>

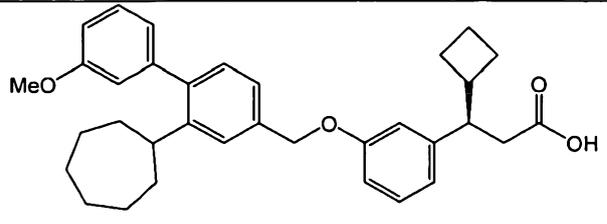
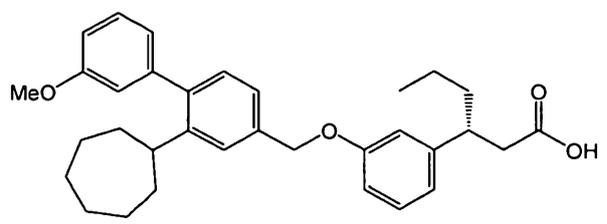
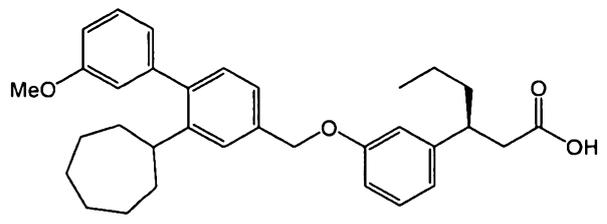
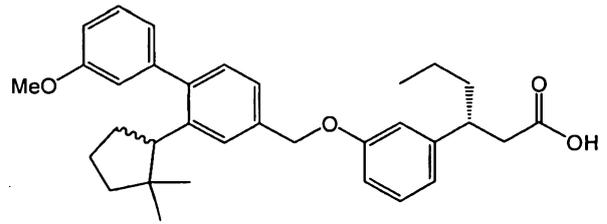
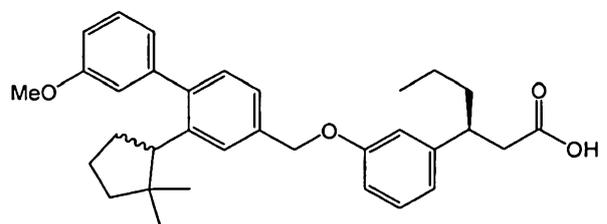
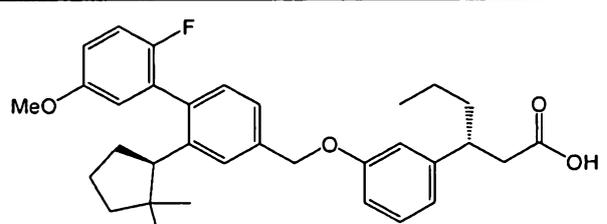
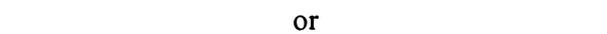
	 <p style="text-align: center;">or</p> 		
<p>78.12</p>	 <p style="text-align: center;">or</p> 	<p style="text-align: center;">++</p>	<p style="text-align: center;">ND</p>
<p>78.13</p>	 <p style="text-align: center;">or</p> 	<p style="text-align: center;">++</p>	<p style="text-align: center;">ND</p>

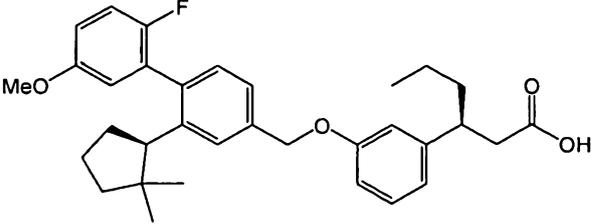
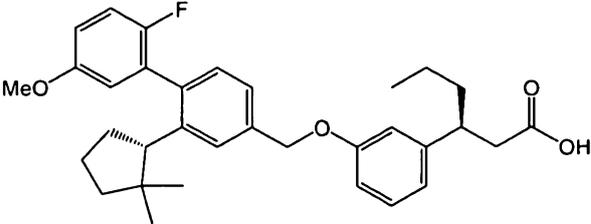
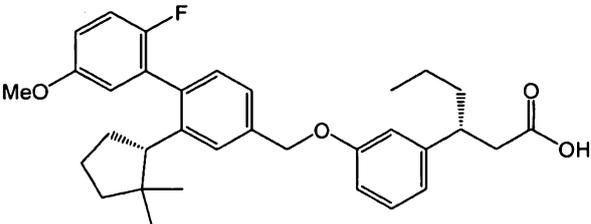
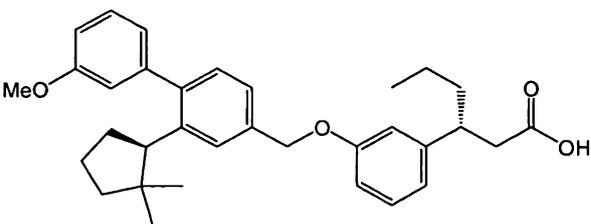
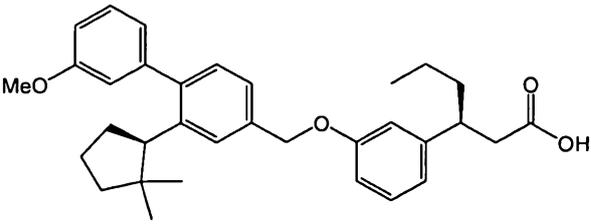
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<p>78.14</p>	<p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	<p style="text-align: center;">++++</p>	<p style="text-align: center;">+++++</p>

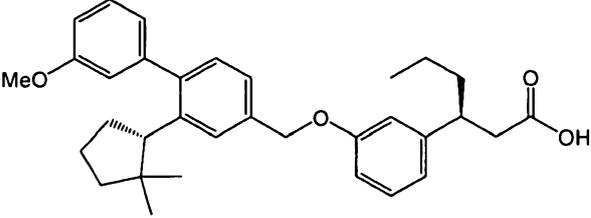
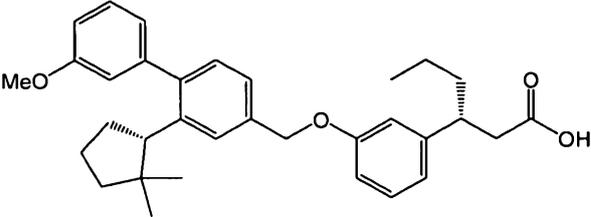
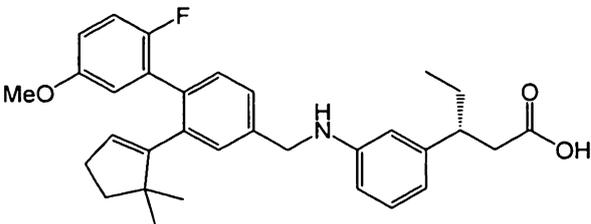
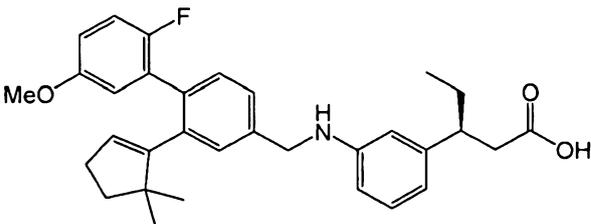
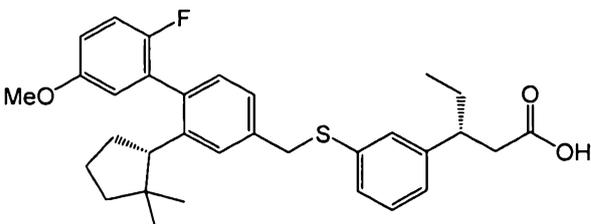
			
79.1	 or 	ND	ND
79.2	 or 	ND	ND
79.3		+++	++++

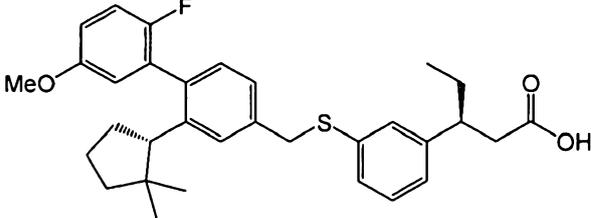
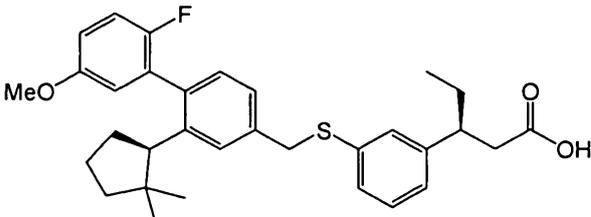
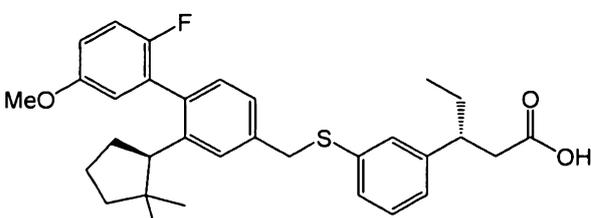
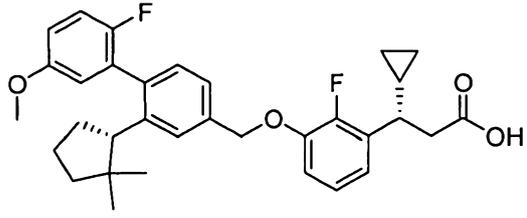
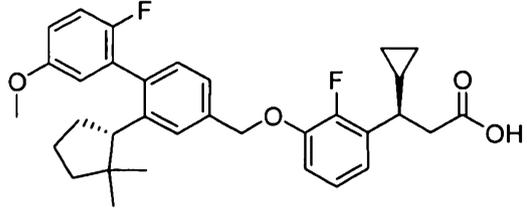
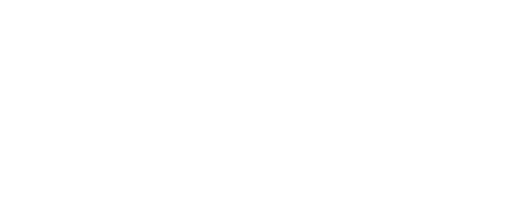
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<p>79.4</p>	<p style="text-align: center;">Diastereomer of 79.3</p>	<p style="text-align: center;">++++</p>	<p style="text-align: center;">+++++</p>
<p>79.5</p>	<p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	<p style="text-align: center;">+++</p>	<p style="text-align: center;">ND</p>

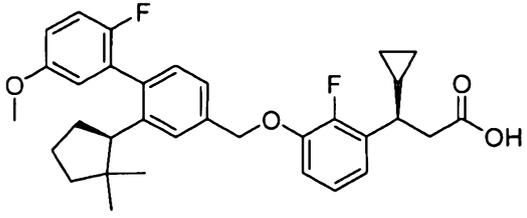
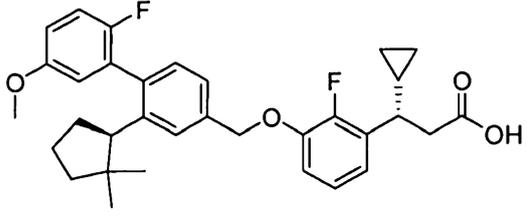
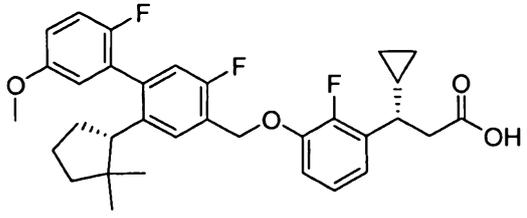
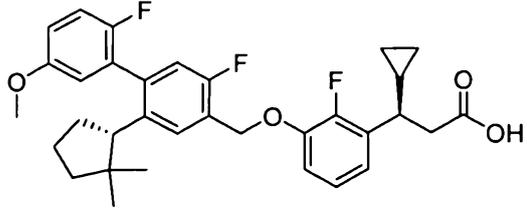
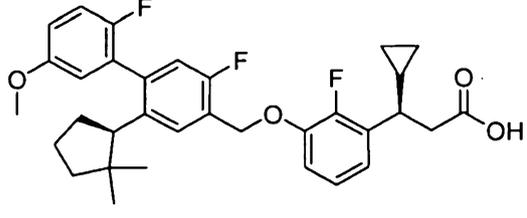
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<p>79.6</p>	<p style="text-align: center;">Diastereomer of 79.5</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">++++</p>
<p>79.7</p>	 <p style="text-align: center;">or</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">++++</p>
<p>79.8</p>	 <p style="text-align: center;">or</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">++++</p>

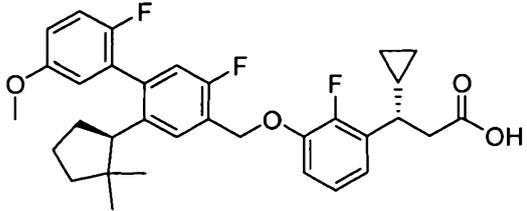
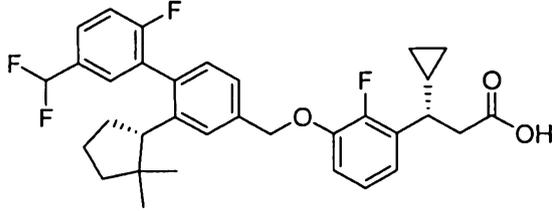
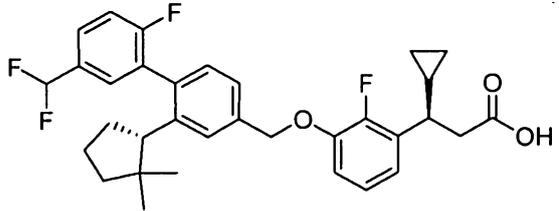
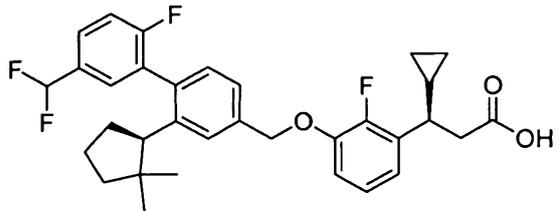
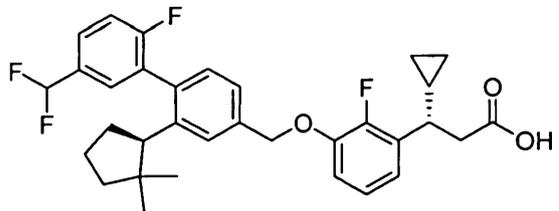
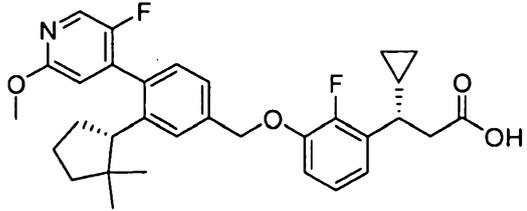
			
80.1	 <p style="text-align: center;">or</p> 	+++	ND
80.2	 <p style="text-align: center;">or</p> 	ND	ND
80.3	 <p style="text-align: center;">or</p> 	+++	ND

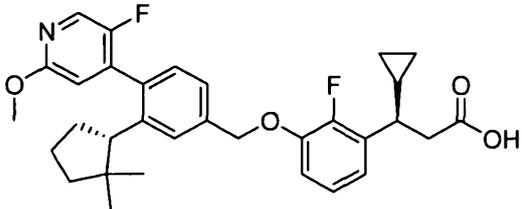
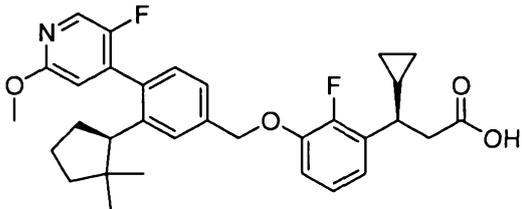
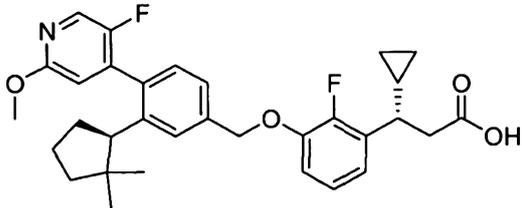
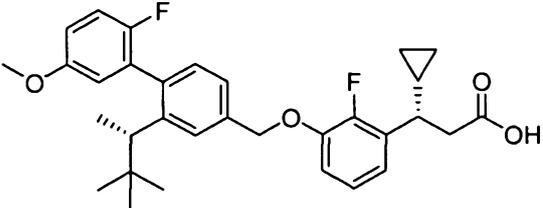
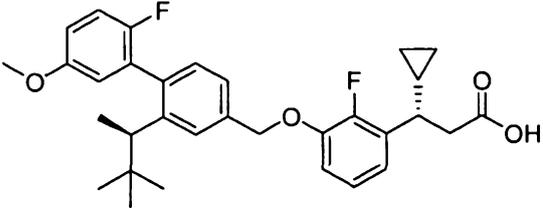
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<p>80.4</p>	<p style="text-align: center;">Diastereomer of 80.3</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">+++++</p>
<p>80.5</p>	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">ND</p>

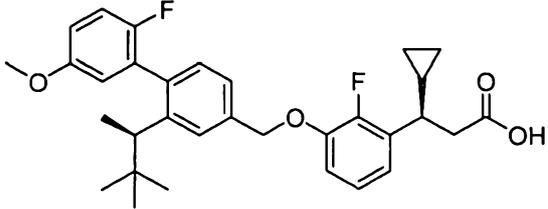
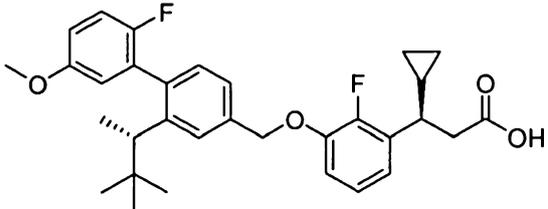
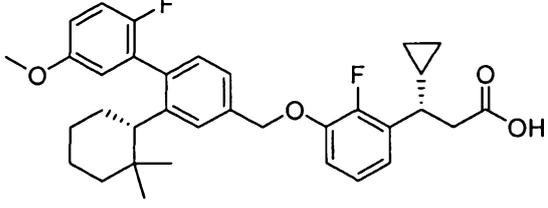
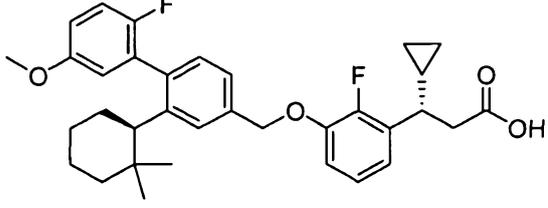
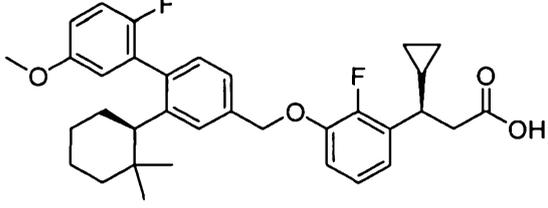
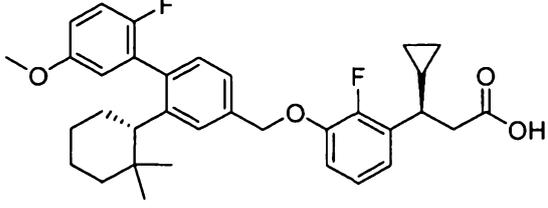
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<p>80.6</p>	<p style="text-align: center;">Diastereomer of 80.5</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">+++++</p>
<p>81</p>	 <p style="text-align: center;">or</p> 	<p style="text-align: center;">+++</p>	<p style="text-align: center;">+</p>
<p>82</p>	 <p style="text-align: center;">or</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">++</p>

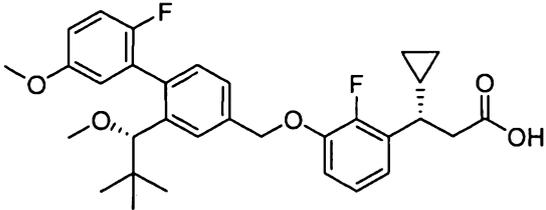
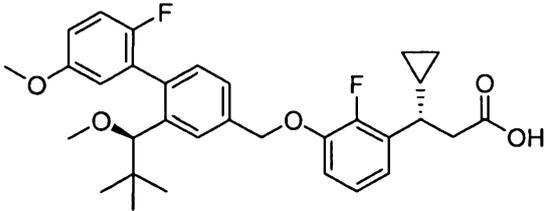
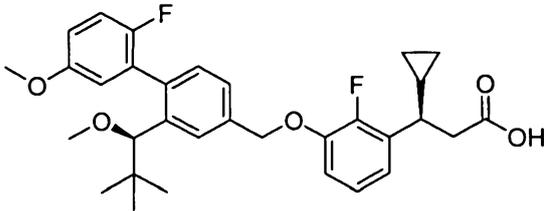
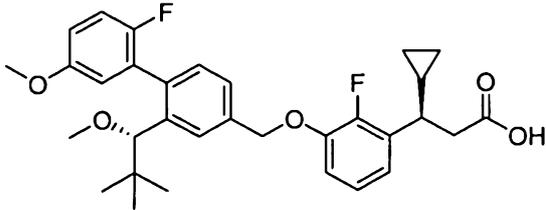
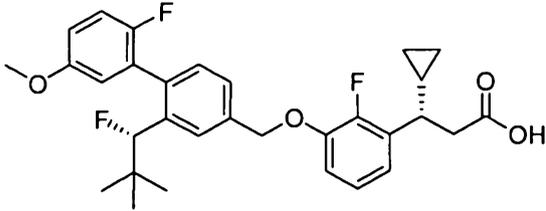
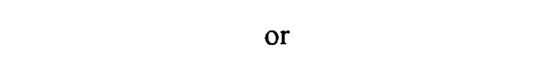
	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 		
<p>83.1</p>	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	<p style="text-align: center;">++++</p>	<p style="text-align: center;">+++++</p>

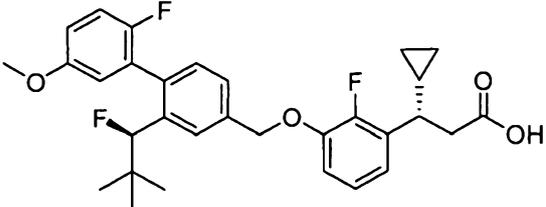
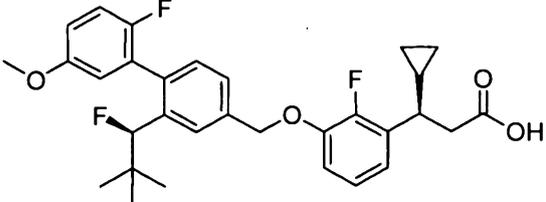
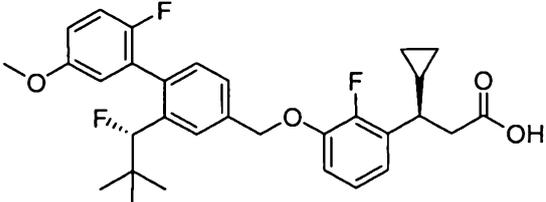
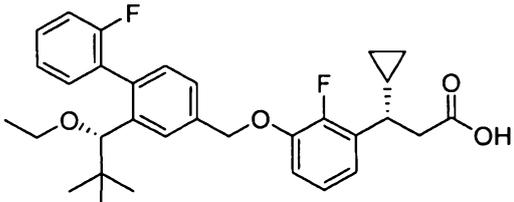
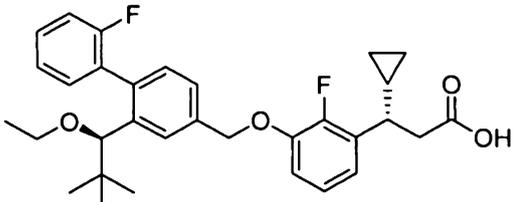
	 <p style="text-align: center;">or</p> 		
<p style="text-align: center;">83.2</p>	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>	<p style="text-align: center;">++++</p>	<p style="text-align: center;">+++++</p>

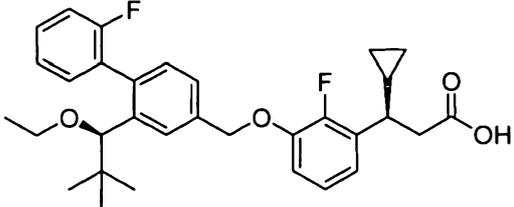
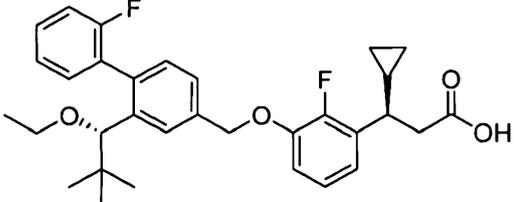
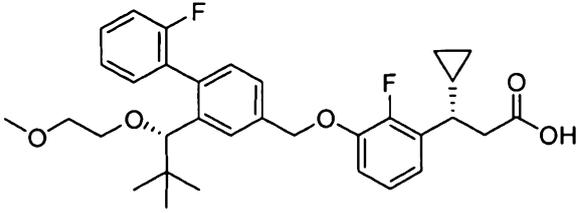
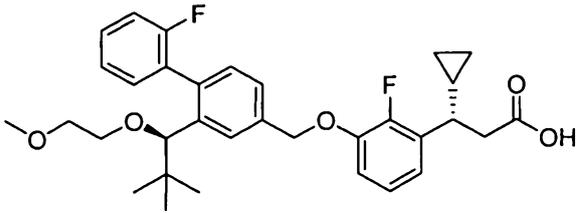
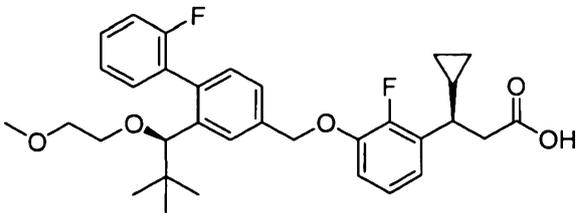
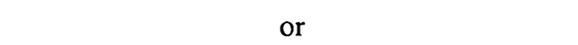
			
<p>83.3</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>+++</p>	<p>++++</p>
<p>83.4</p>		<p>++++</p>	<p>+++++</p>

	<p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 		
<p>83.5</p>	<p style="text-align: center;">Diastereomer of 83.4</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">++++</p>
<p>83.6</p>	<p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	<p style="text-align: center;">+++</p>	<p style="text-align: center;">+++++</p>

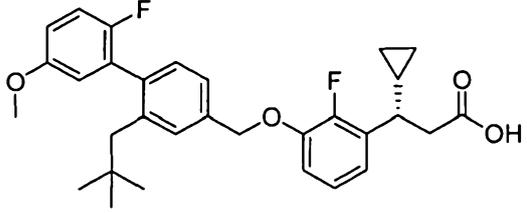
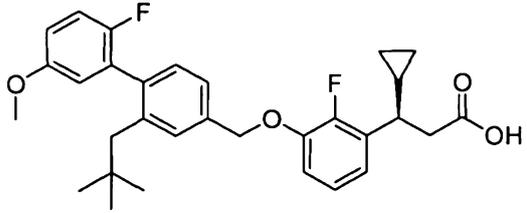
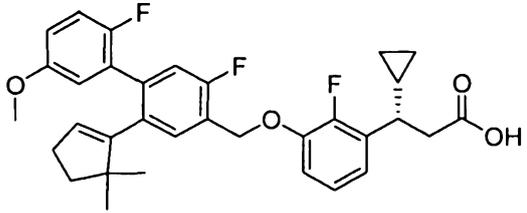
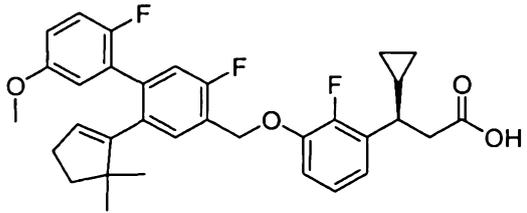
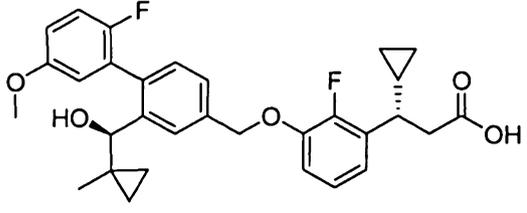
	 <p style="text-align: center;">or</p> 		
<p>83.7</p>	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	<p style="text-align: center;">+++</p>	<p style="text-align: center;">+++++</p>

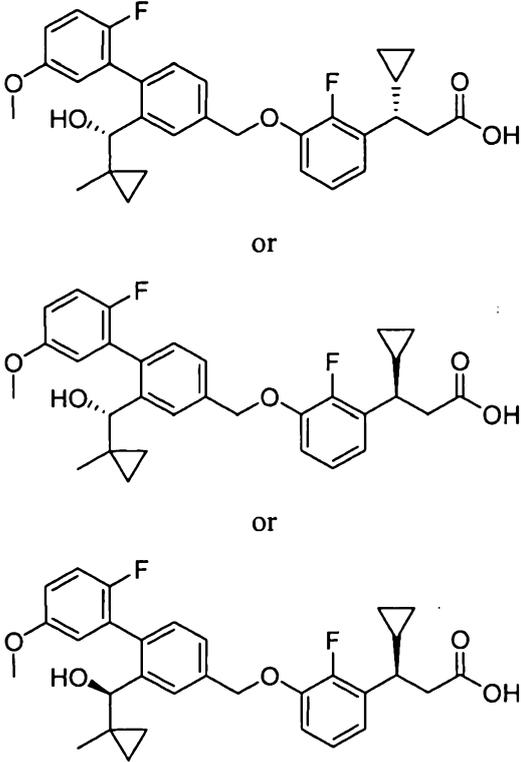
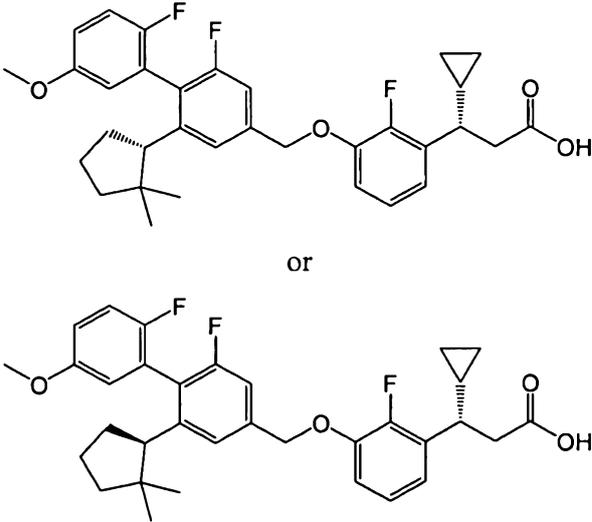
<p>83.8</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>+++</p>	<p>+++++</p>
<p>83.9</p>	 <p>or</p> 	<p>+++</p>	<p>+++++</p>

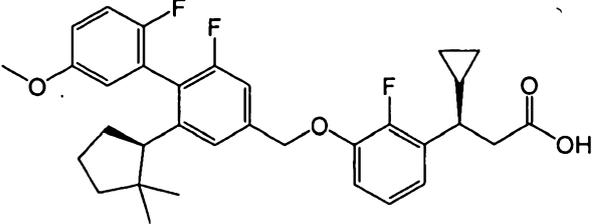
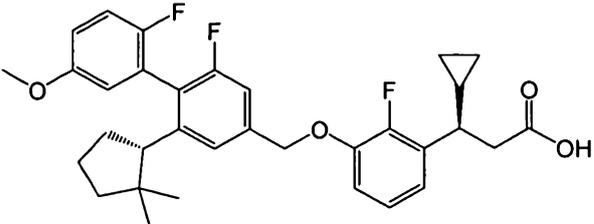
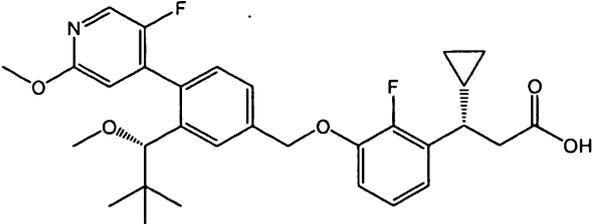
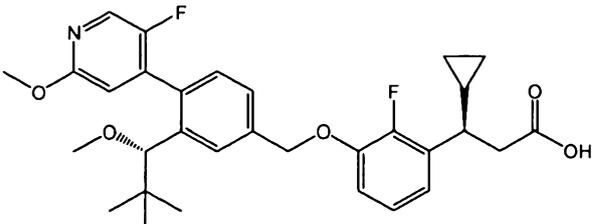
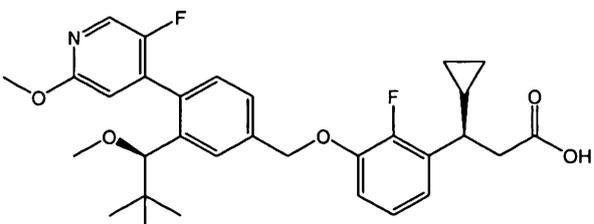
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<p>83.10</p>	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	<p style="text-align: center;">+++</p>	<p style="text-align: center;">++++</p>

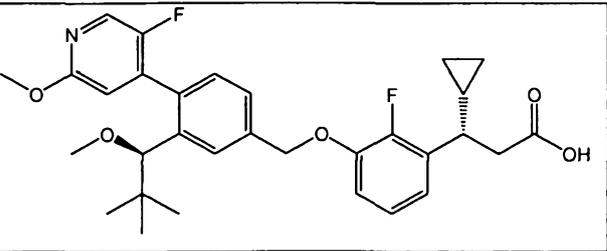
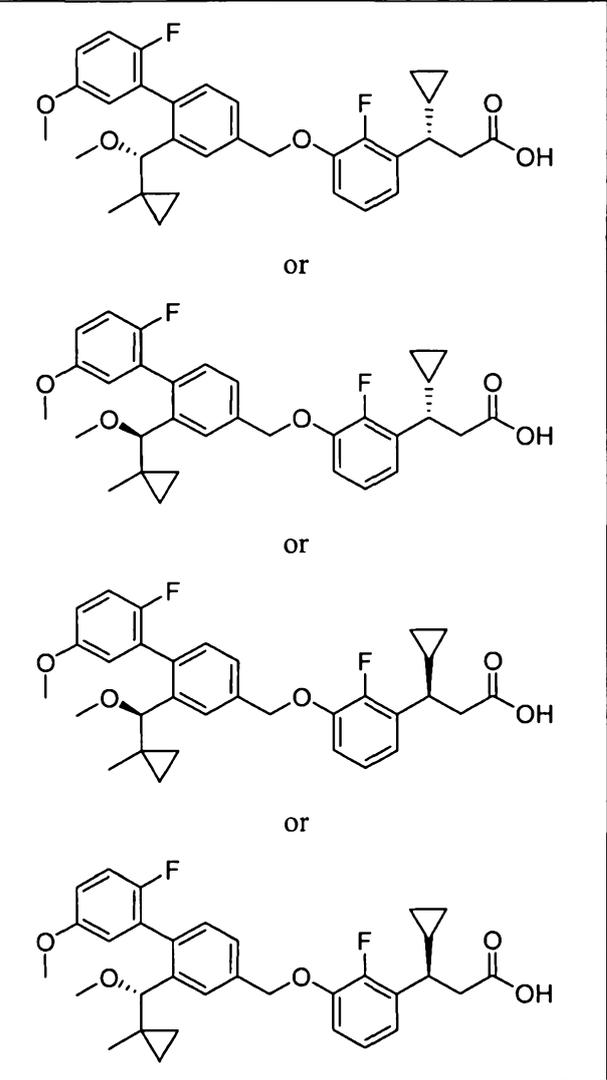
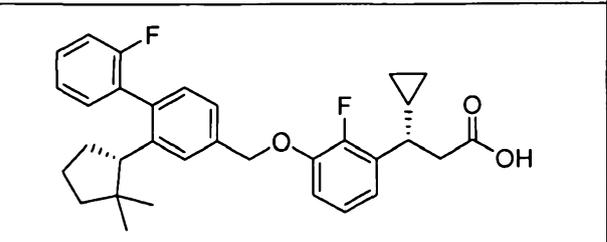
	 <p style="text-align: center;">or</p> 		
<p>83.11</p>	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	<p style="text-align: center;">+++</p>	<p style="text-align: center;">++++</p>

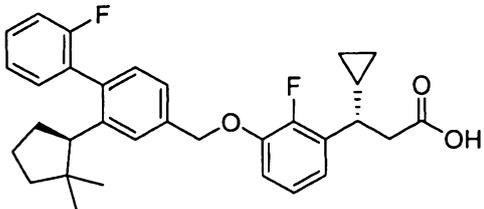
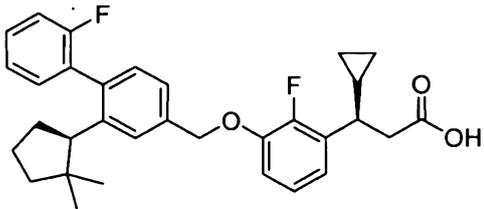
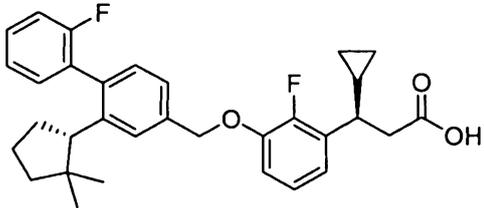
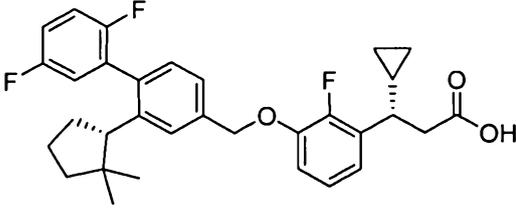
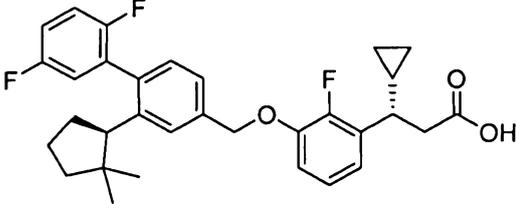
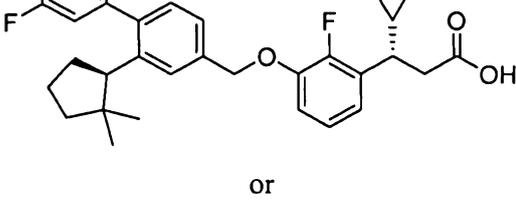
83.12	<p style="text-align: center;">or</p>	+++	++++
83.13	Diastereomer of 83.3	++	ND
83.14	<p style="text-align: center;">or</p>	+++	+++++

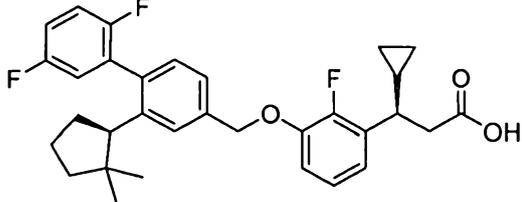
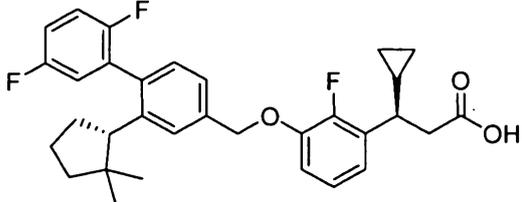
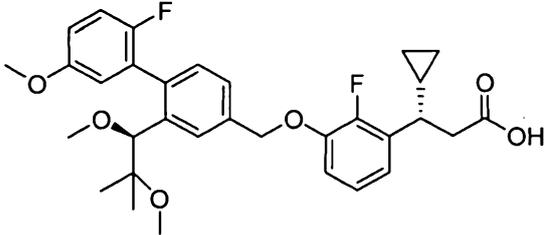
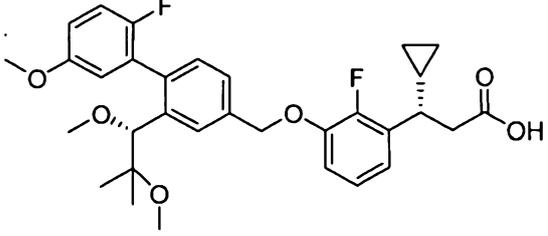
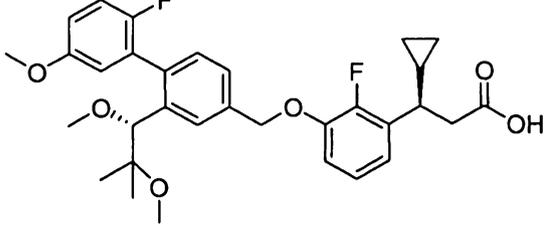
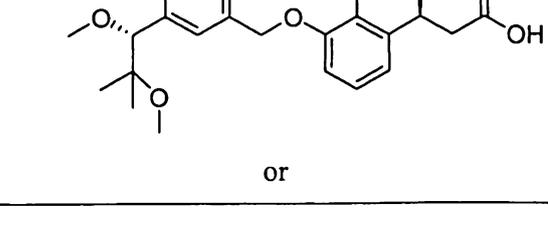
<p>83.15</p>	 <p>or</p> 	<p>+++</p>	<p>+++++</p>
<p>83.16</p>	 <p>or</p> 	<p>+++</p>	<p>++++</p>
<p>83.17</p>	<p>Diastereomer of 83.1</p>	<p>+++</p>	<p>ND</p>
<p>83.18</p>	 <p>or</p>	<p>++</p>	<p>ND</p>

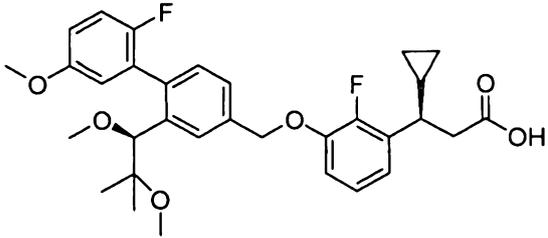
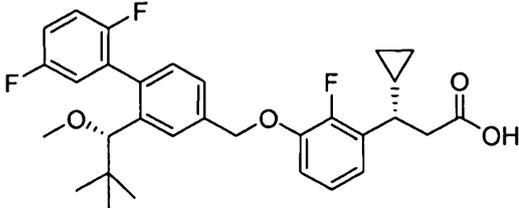
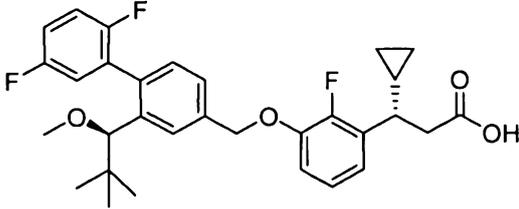
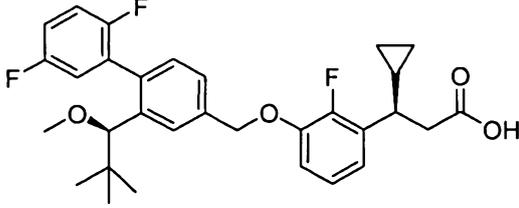
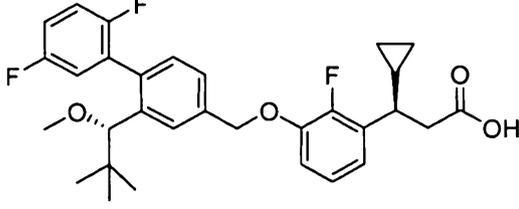
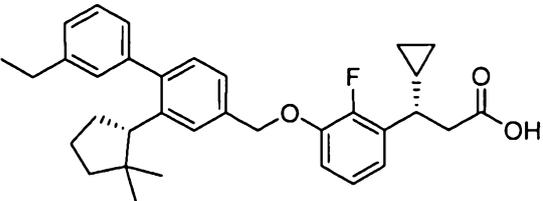
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<p>83.19</p>	<p style="text-align: center;">Diastereomer of 83.18</p>	<p style="text-align: center;">++</p>	<p style="text-align: center;">ND</p>
<p>83.20</p>	 <p style="text-align: center;">or</p> <p style="text-align: center;">or</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">+++++</p>

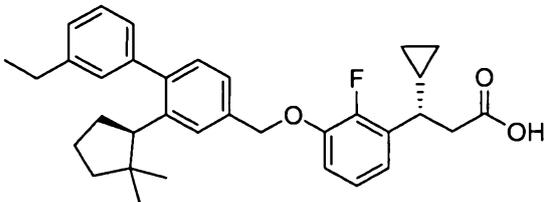
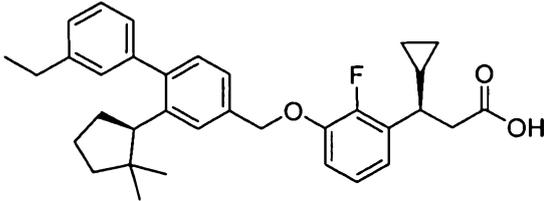
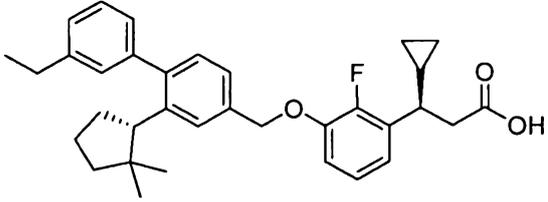
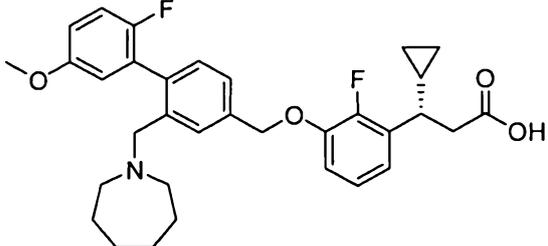
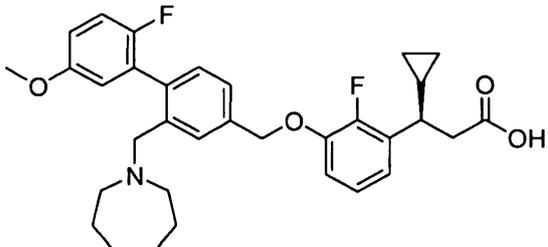
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<p>83.21</p>	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>	<p style="text-align: center;">++++</p>	<p style="text-align: center;">+++++</p>

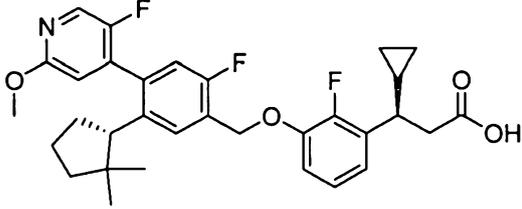
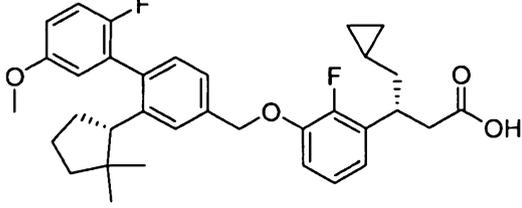
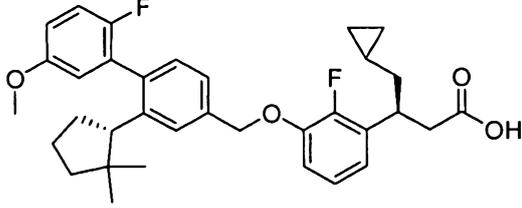
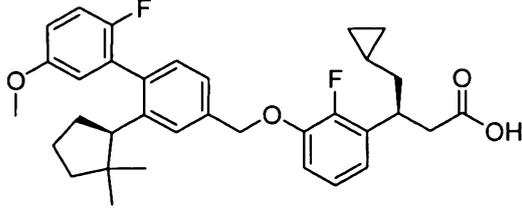
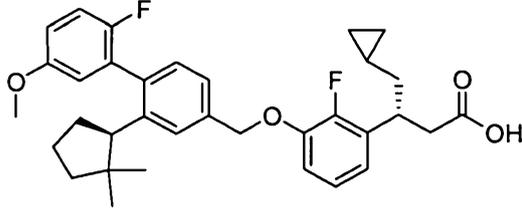
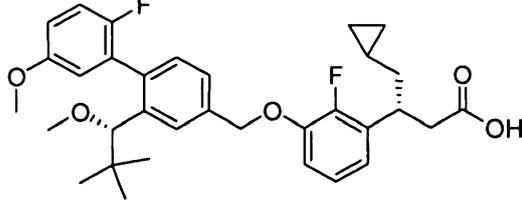
			
<p>83.22</p>		<p>++++</p>	<p>+++++</p>
<p>83.23</p>		<p>+++</p>	<p>ND</p>

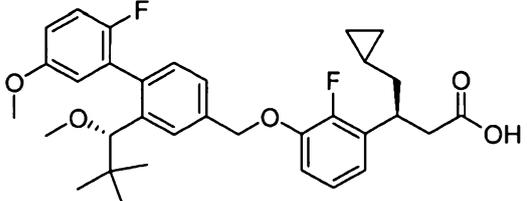
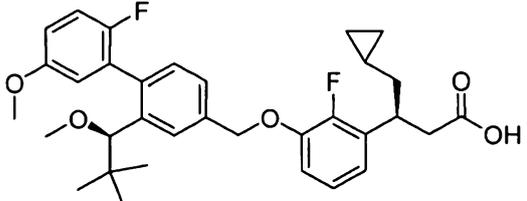
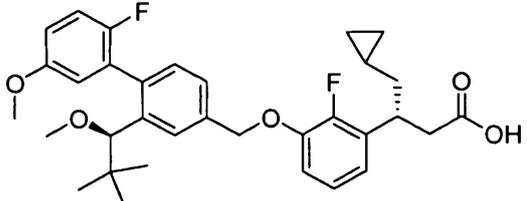
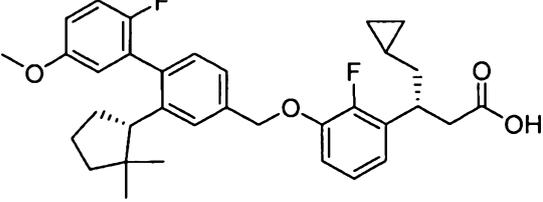
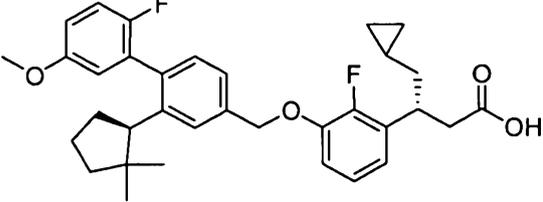
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<p>83.24</p>	<p style="text-align: center;">Diastereomer of 83.20</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">++++</p>
<p>83.25</p>	<p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	<p style="text-align: center;">+++</p>	<p style="text-align: center;">++++</p>

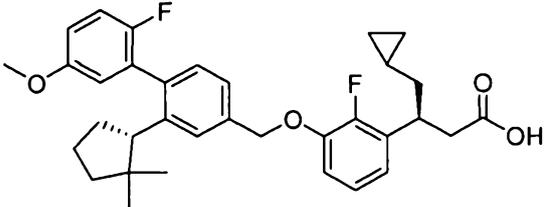
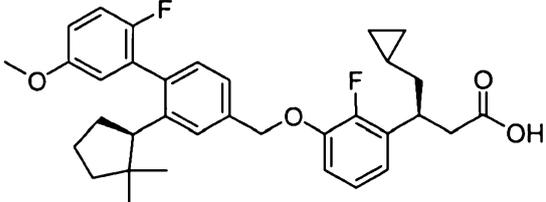
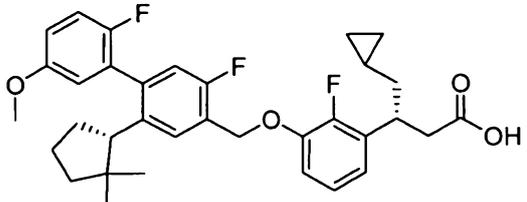
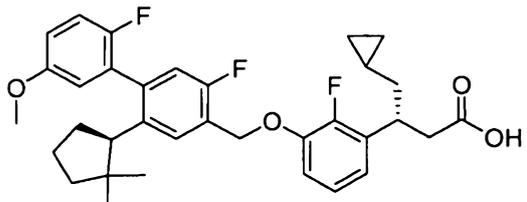
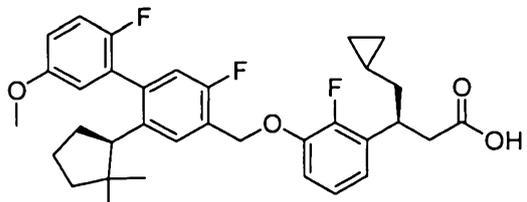
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<p>83.26</p>	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	<p style="text-align: center;">+++</p>	<p style="text-align: center;">++++</p>

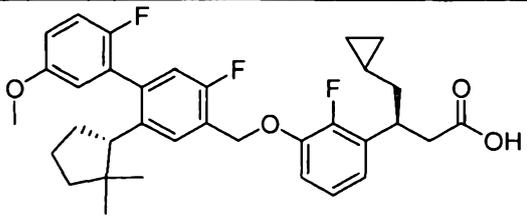
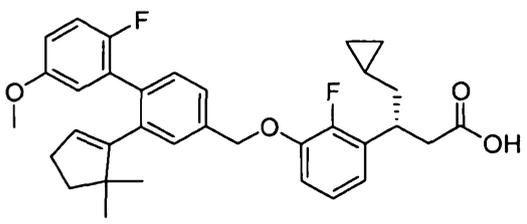
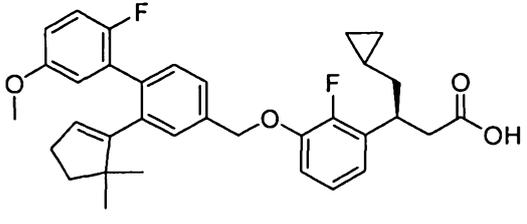
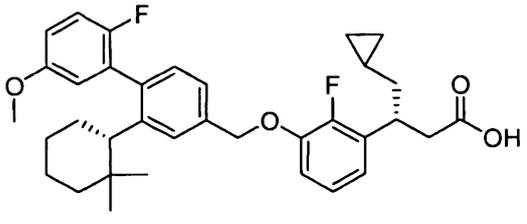
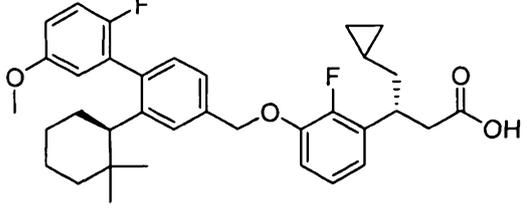
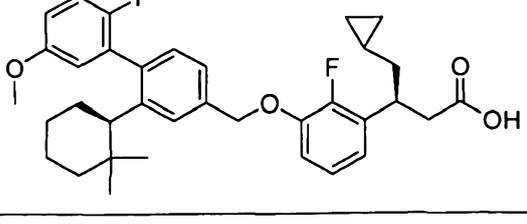
			
<p>83.27</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>+++</p>	<p>++++</p>
<p>83.28</p>		<p>+++</p>	<p>++++</p>

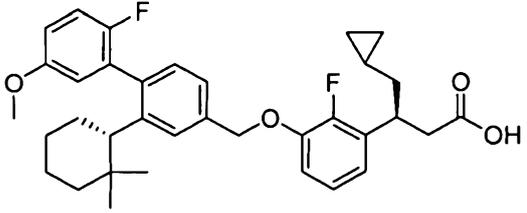
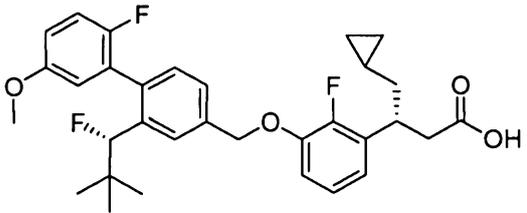
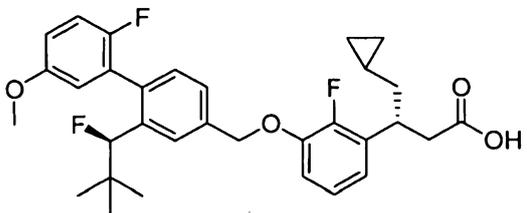
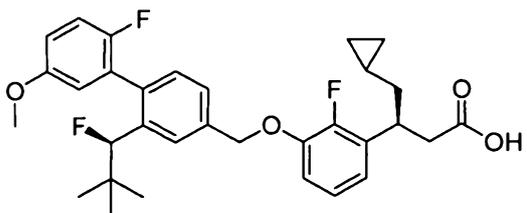
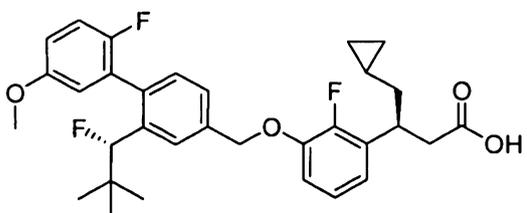
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<p>83.29</p>	 <p style="text-align: center;">Or</p> 	<p style="text-align: center;">++</p>	<p style="text-align: center;">+++</p>

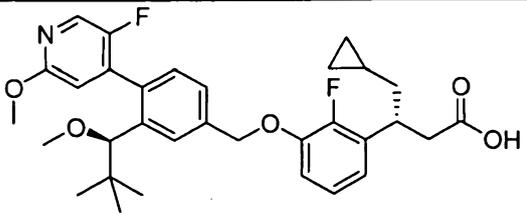
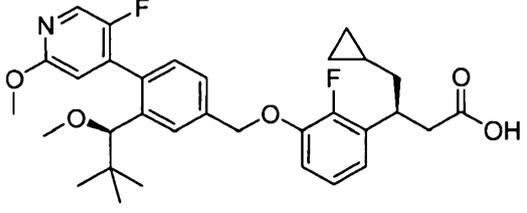
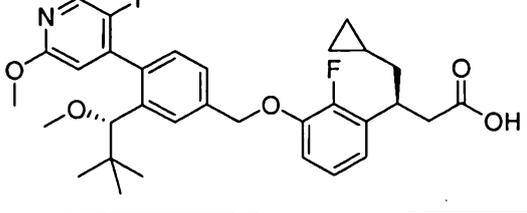
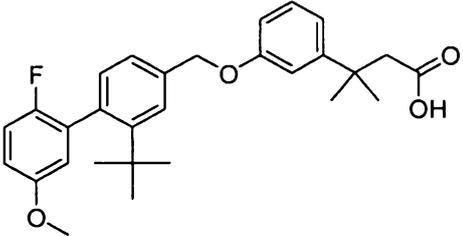
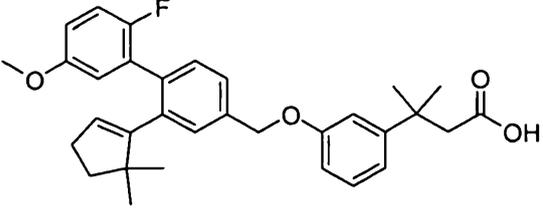
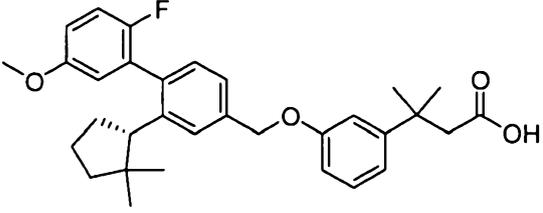
			
<p>84.1</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>+++</p>	<p>+++++</p>
<p>84.2</p>		<p>+++</p>	<p>+++++</p>

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<p style="text-align: center;">84.3</p>	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	<p style="text-align: center;">+++</p>	<p style="text-align: center;">+++++</p>

	 <p style="text-align: center;">or</p> 		
<p>84.4</p>	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>	<p style="text-align: center;">+++</p>	<p style="text-align: center;">+++++</p>

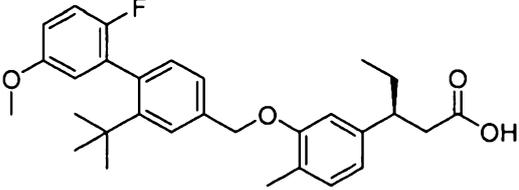
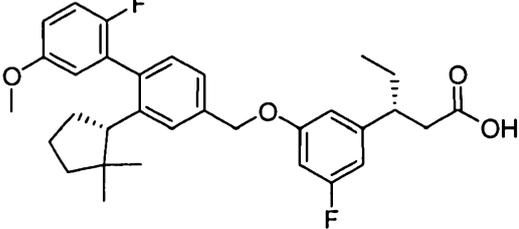
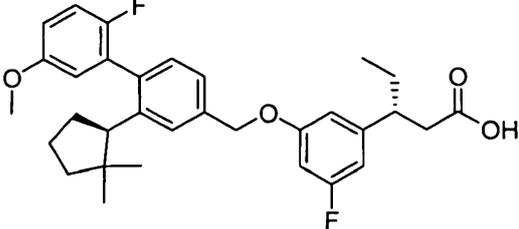
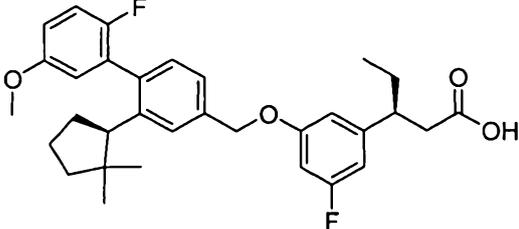
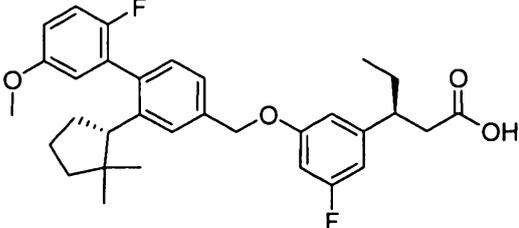
			
84.5	 or 	+++	++++
84.6	 or  or 	+++	+++++

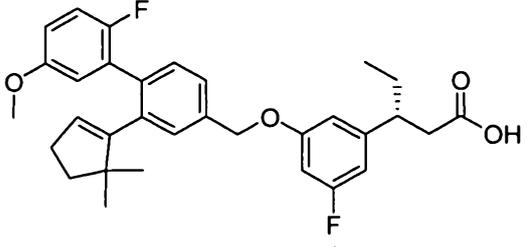
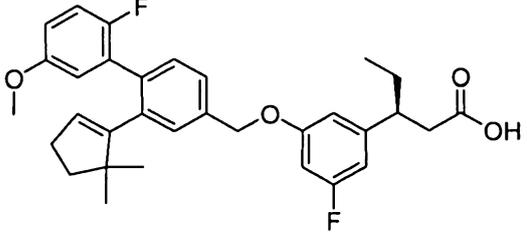
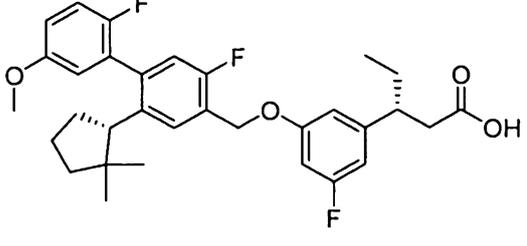
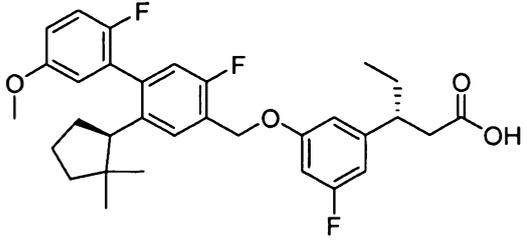
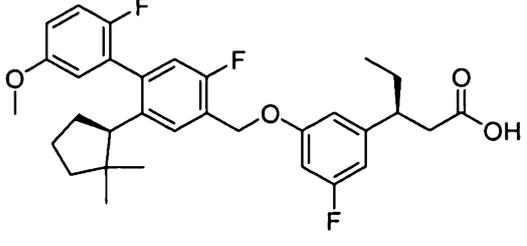
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<p style="text-align: center;">84.7</p>	<p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	<p style="text-align: center;">++++</p>	<p style="text-align: center;">+++++</p>

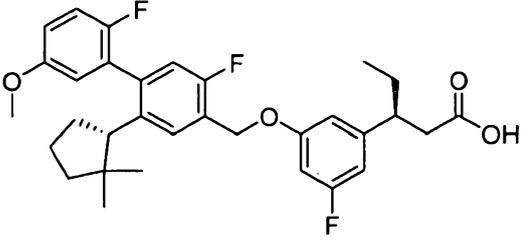
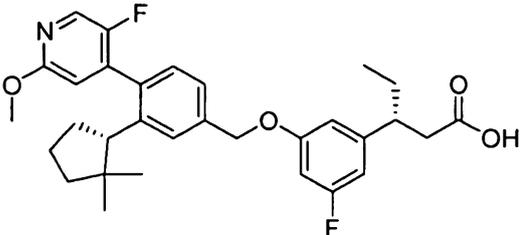
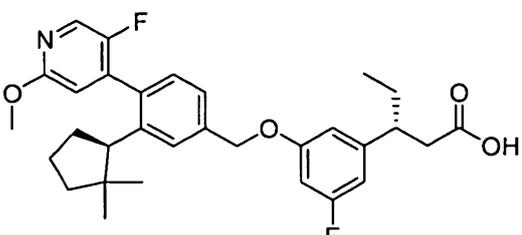
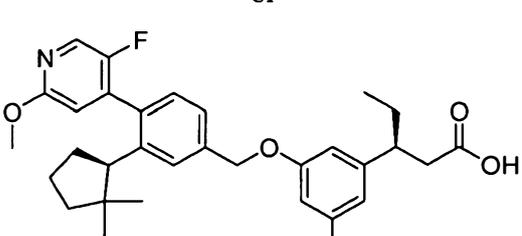
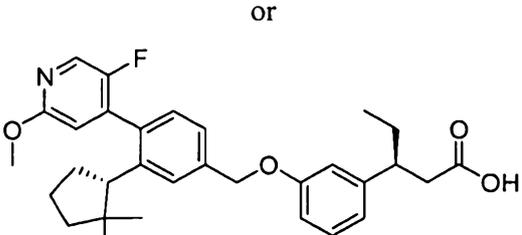
	 <p>or</p>  <p>or</p> 		
85.1		+++	+++
85.2		+++	++++
85.3		+++	++++

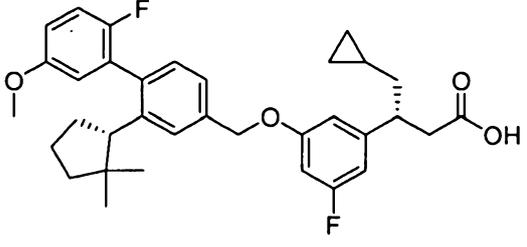
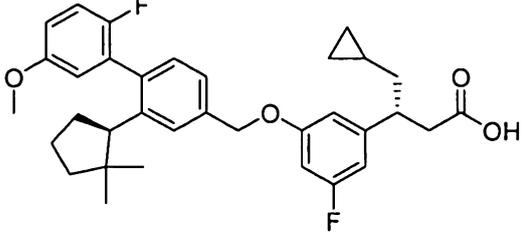
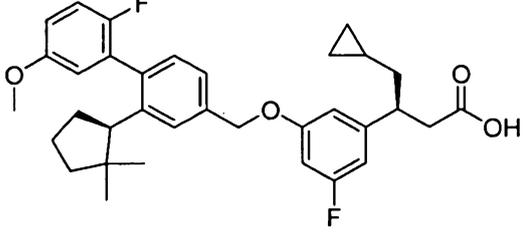
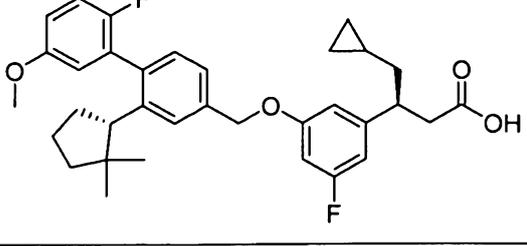
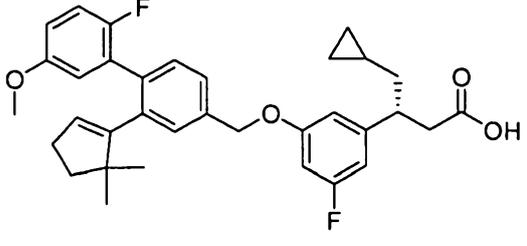
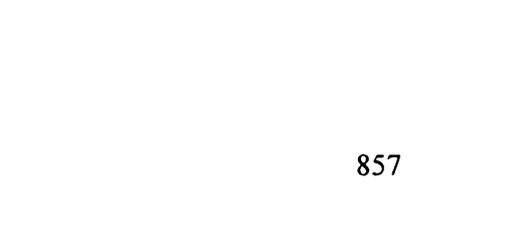
	<p>or</p>		
85.4	<p>or</p>	+++	++++
85.5	<p>or</p>	+++	++++
85.6		+++	++++

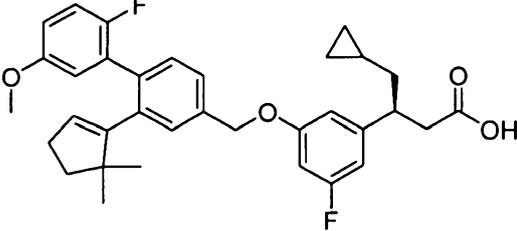
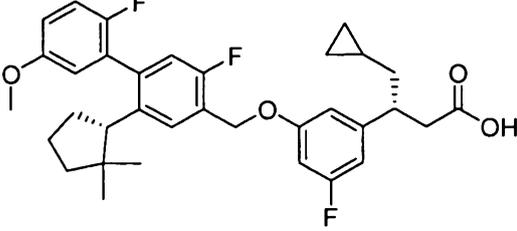
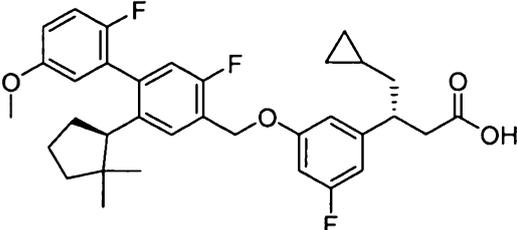
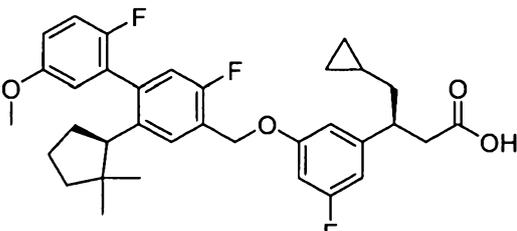
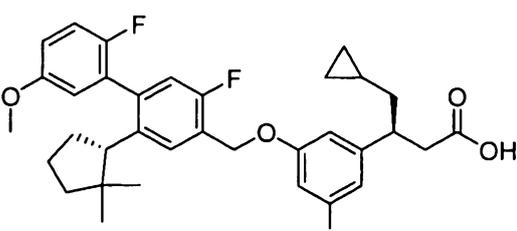
	<p>or</p>		
86.1	<p>or</p>	+++	+++
86.2	<p>or</p>	++	ND
87		+++	+++

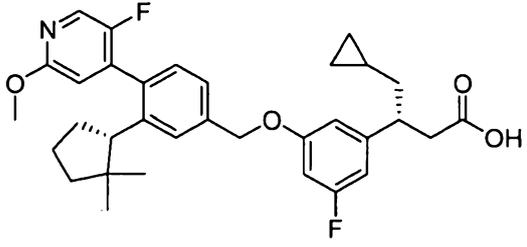
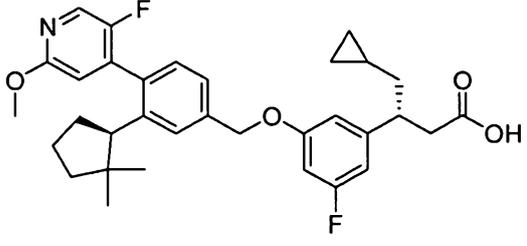
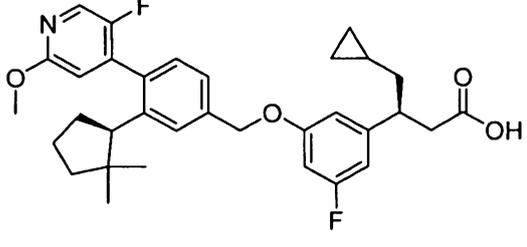
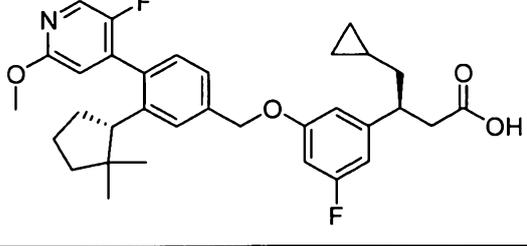
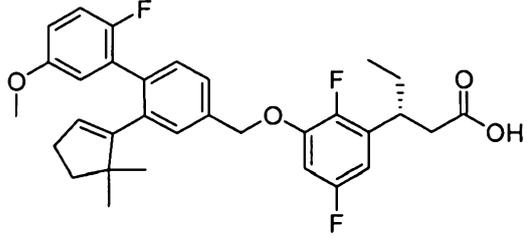
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<p>88.1</p>			
	<p>or</p>		
			
	<p>or</p>	<p>++++</p>	<p>+++++</p>
			
<p>or</p>			
			

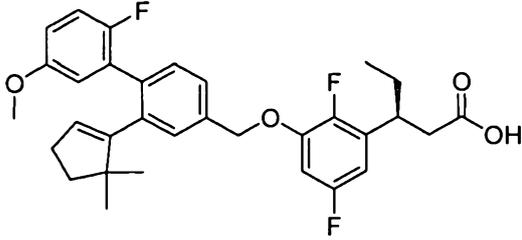
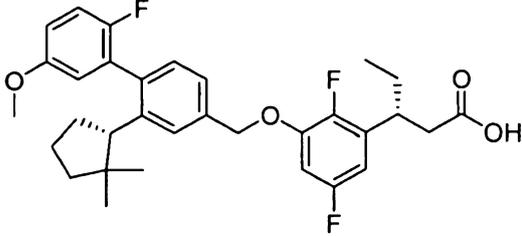
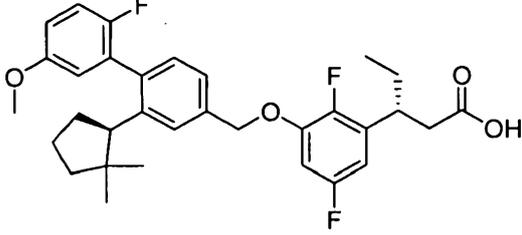
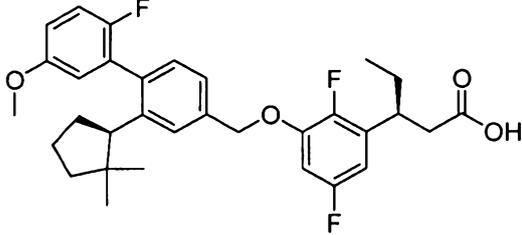
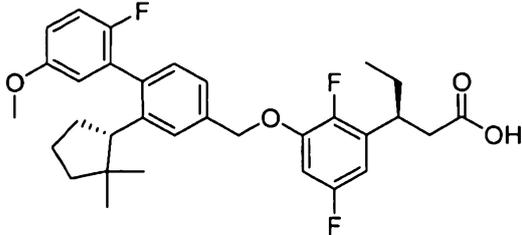
<p>88.2</p>	 <p>or</p> 	<p>+++</p>	<p>++++</p>
<p>88.3</p>	 <p>or</p>  <p>or</p> 	<p>+++</p>	<p>+++++</p>

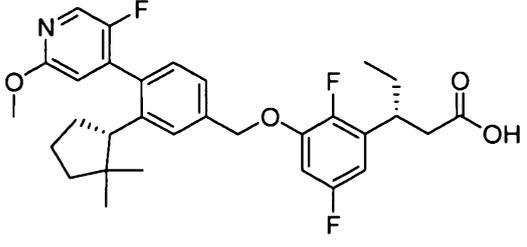
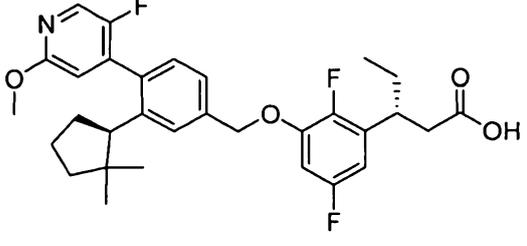
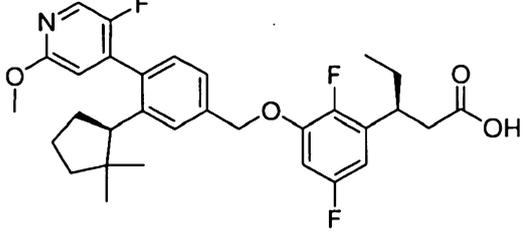
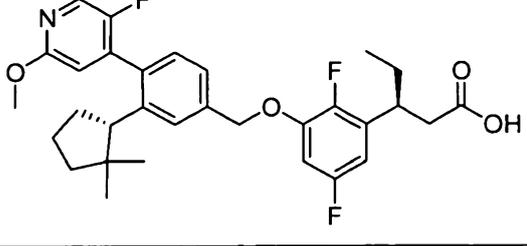
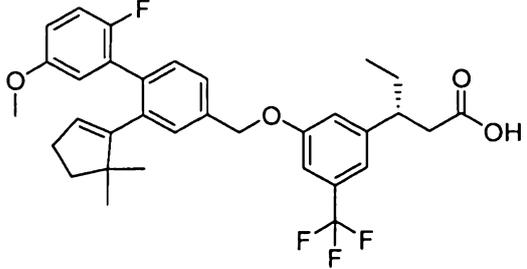
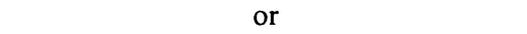
			
<p>88.4</p>			
	<p>or</p> 		
	<p>or</p> 		
	<p>or</p> 	<p>+++</p>	<p>+++++</p>

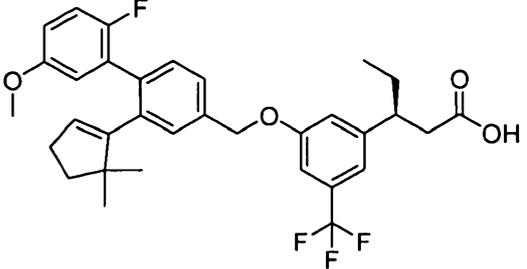
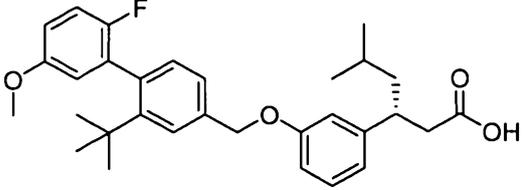
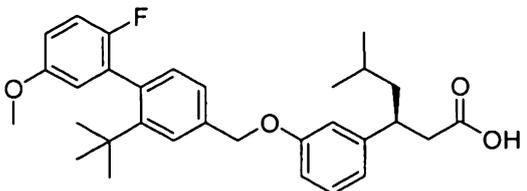
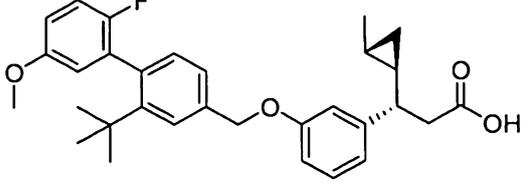
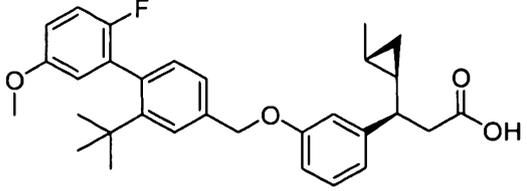
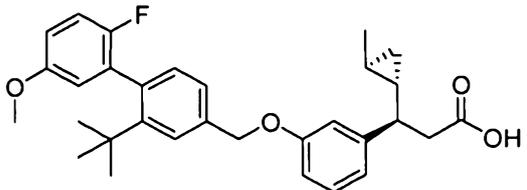
<p>89.1</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>++++</p>	<p>+++++</p>
<p>89.2</p>	 <p>or</p> 	<p>+++</p>	<p>++++</p>

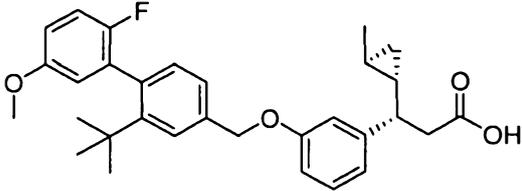
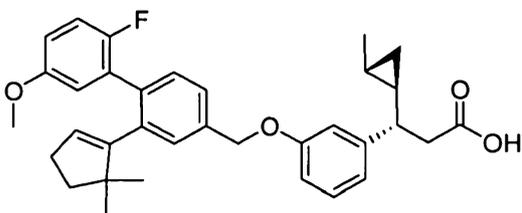
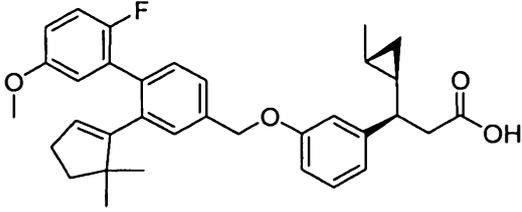
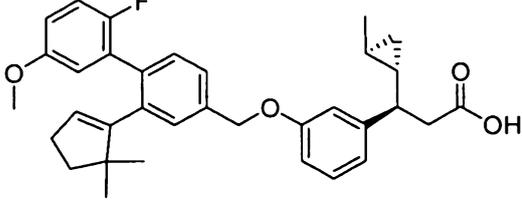
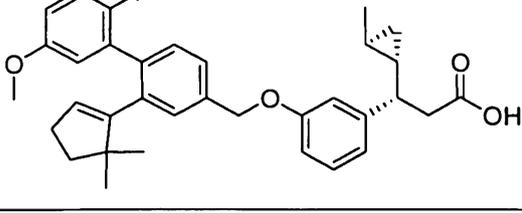
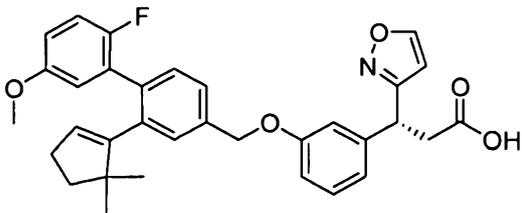
			
<p>89.3</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>+++</p>	<p>+++++</p>

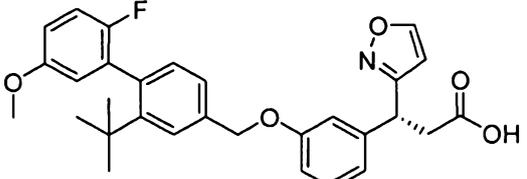
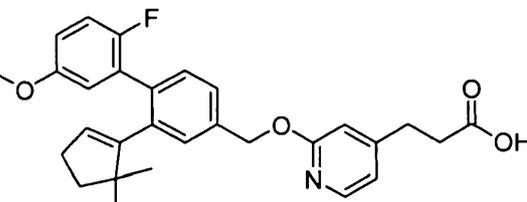
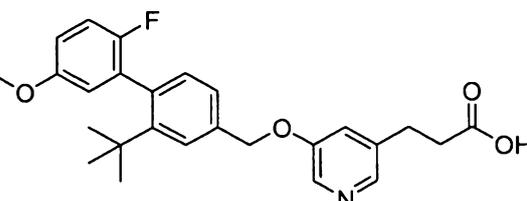
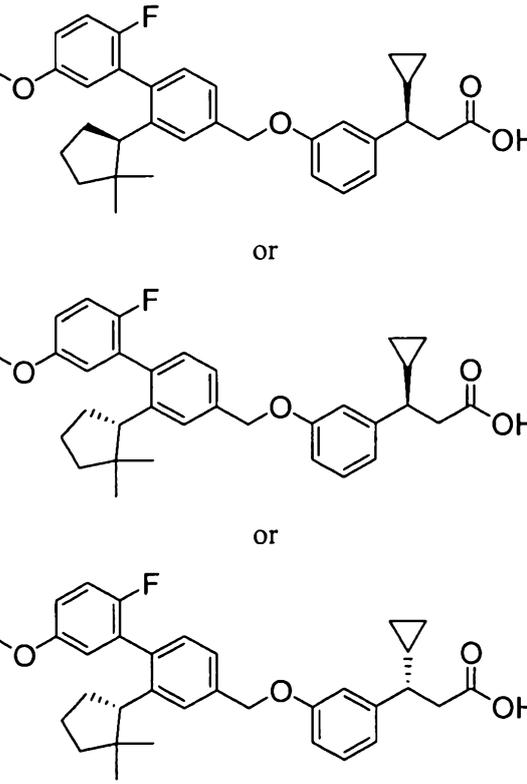
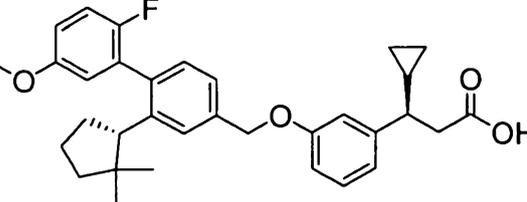
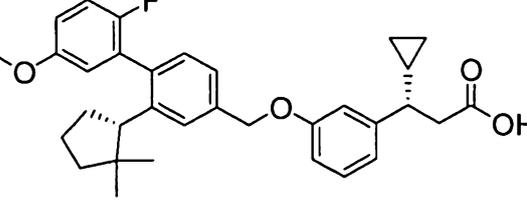
<p>89.4</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>+++</p>	<p>+++++</p>
<p>90.1</p>	 <p>or</p> 	<p>+++</p>	<p>++++</p>

			
<p>90.2</p>			
	<p>or</p>		
			
	<p>or</p>	<p>+++</p>	<p>+++++</p>
			
<p>or</p>			
			

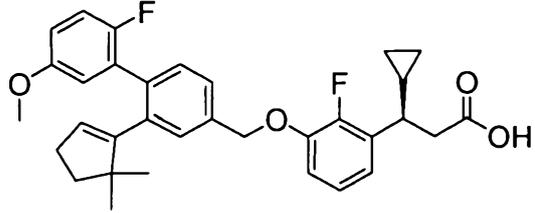
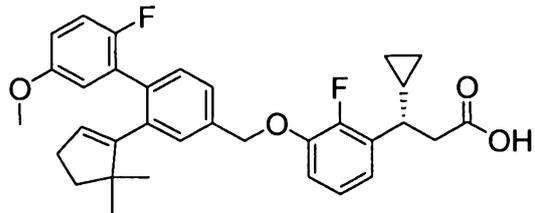
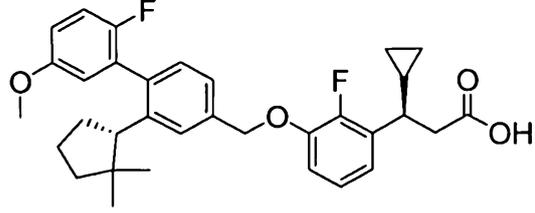
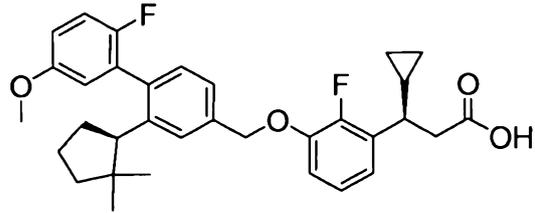
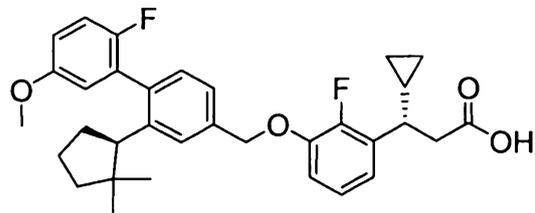
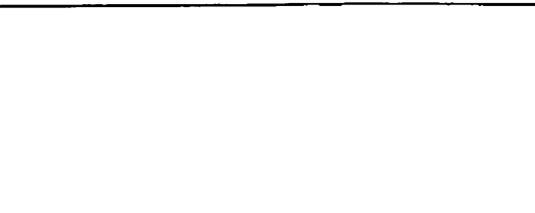
<p>90.3</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>+++</p>	<p>+++++</p>
<p>91</p>	 <p>or</p> 	<p>+++</p>	<p>++++</p>

			
<p>92</p>	 <p>or</p> 	<p>++</p>	<p>ND</p>
<p>93.1</p>	 <p>or</p>  <p>or</p> 	<p>+++</p>	<p>++++</p>

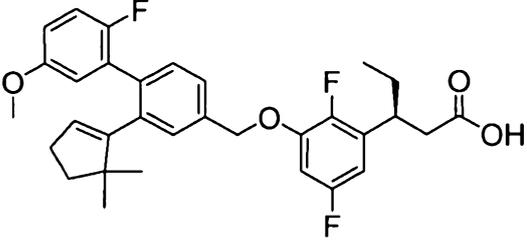
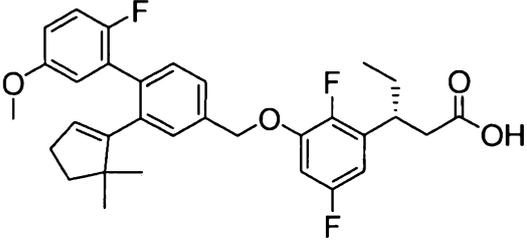
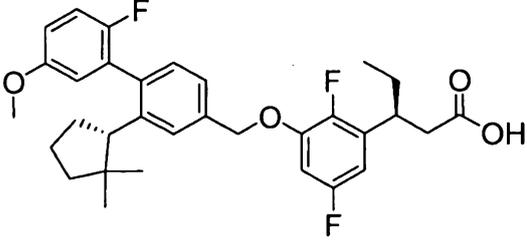
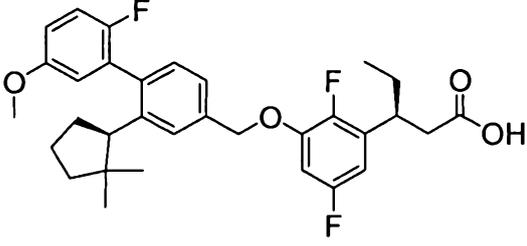
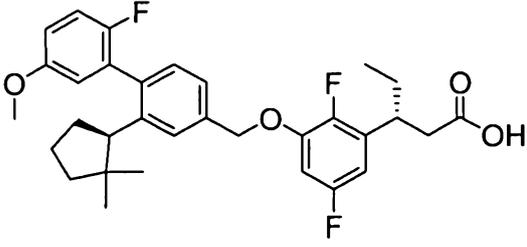
			
<p>93.2</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>+++</p>	<p>++++</p>
<p>94.1</p>		<p>++</p>	<p>ND</p>

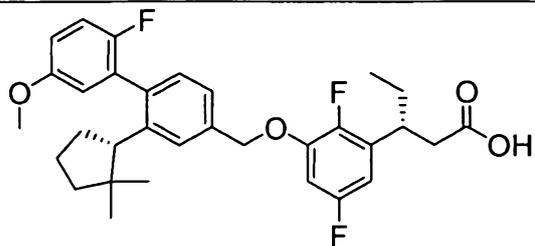
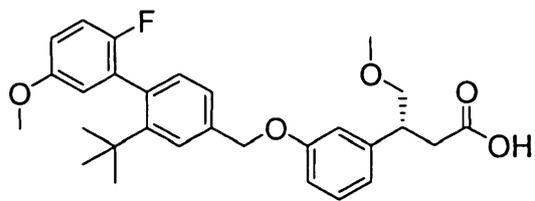
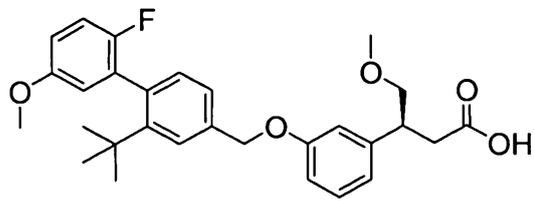
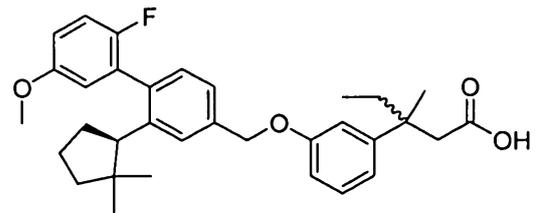
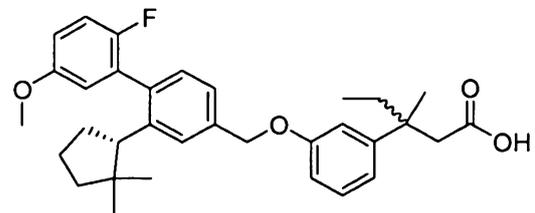
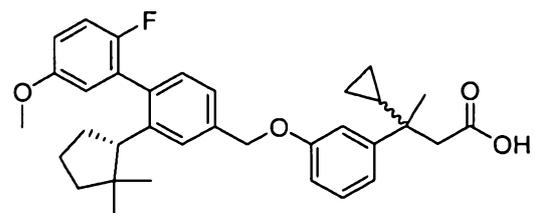
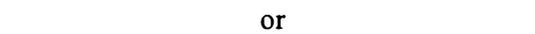
94.2		++	ND
95		+++	+++
96		++	ND
97.1	Enantiomer of 14	++	ND
97.2	 <p style="text-align: center;">or</p>  <p style="text-align: center;">or</p> 	++	ND

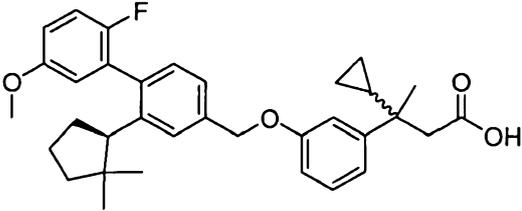
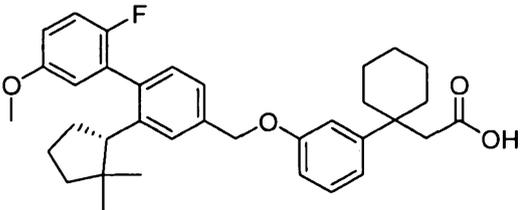
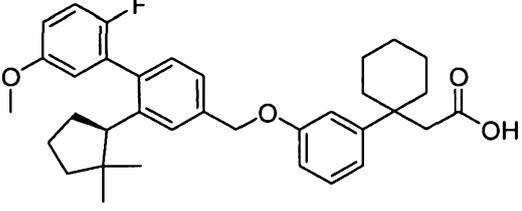
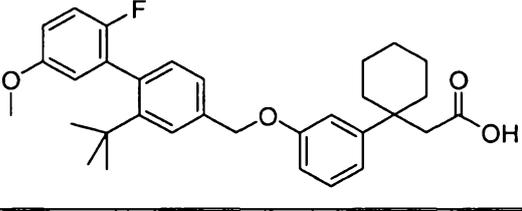
	<p>or</p>			
97.3	Diastereomer of 97.2	+++	++++	
98.1	<p>or</p> <p>or</p> <p>or</p>	+++	ND	
	98.2	Diastereomer of 98.1	++	ND

<p>99.1</p>	 <p>or</p> 	<p>++</p>	<p>ND</p>
<p>99.2</p>	 <p>or</p>  <p>or</p>  <p>or</p> 	<p>+++</p>	<p>++++</p>

99.3	Diastereomer of 99.2	++	ND
100.1	<p>or</p> <p>or</p> <p>or</p>	++	ND
	Diastereomer of 100.1	+++	ND

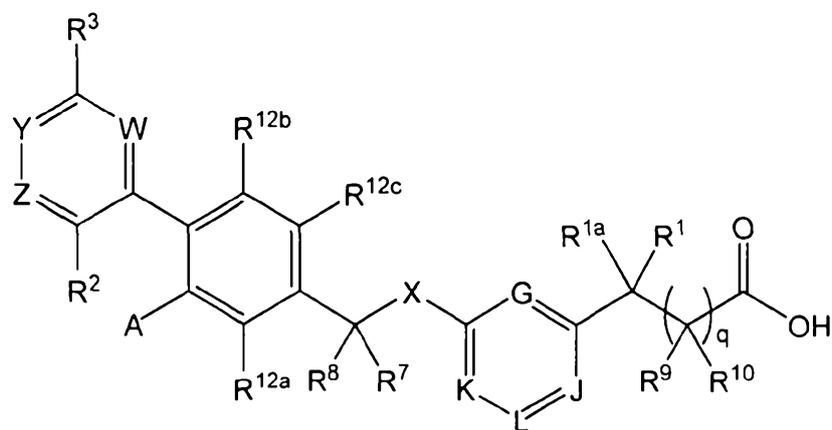
<p>101.1</p>	 <p>or</p> 	<p>++</p>	<p>ND</p>
<p>101.2</p>	 <p>or</p>  <p>or</p> 	<p>+++</p>	<p>ND</p>

			
102	 or 	+++	ND
103	 or 	+++	++++
104	 or 	+++	++++

			
105.1	 or 	+++	++++
105.2		++	ND
<p>^a When present, the “” bond indicates a mixture of stereoisomers are present in the exemplary compound or indicates a mixture of cis and trans isomers when attached to a double bond.</p> <p>^b Aequorin assay data</p> <p>^c EC₅₀ Ranges:</p> <p style="margin-left: 40px;">+ EC₅₀ > 10 μM</p> <p style="margin-left: 40px;">++ 1 μM ≤ EC₅₀ ≤ 10 μM</p> <p style="margin-left: 40px;">+++ 0.1 μM ≤ EC₅₀ < 1 μM</p> <p style="margin-left: 40px;">++++ 0.01 μM ≤ EC₅₀ < 0.1 μM</p> <p style="margin-left: 40px;">+++++ EC₅₀ < 0.01 μM</p> <p>^d Inositol phosphate assay data</p> <p>^e ND means not determined</p>			

CLAIMS

1. A compound of formula I:



I

or a pharmaceutically acceptable salt, stereoisomer, C₁-C₆ alkyl ester, or a mixture thereof, wherein

G is selected from N or CR^{11a};

J is selected from N or CR^{11b};

L is selected from N or CR^{11c};

K is selected from N or CR^{11d};

wherein 0 or 1 of G, J, L, and K is N;

A is selected from -(C₁-C₁₂)alkyl; -(C₂-C₁₂)alkenyl; -(C₁-C₁₂)alkyl-O-(C₁-C₄)alkyl; -(C₁-C₁₂)alkyl-OH; -(C₁-C₁₂)alkyl-O-(C₂-C₄)alkenyl; -(C₂-C₁₂)alkenyl-O-(C₁-C₄)alkyl; -(C₂-C₁₂)alkenyl-OH; -(C₂-C₁₂)alkenyl-O-(C₂-C₄)alkenyl; -O-(C₁-C₁₂)alkyl; -O-(C₂-C₁₂)alkenyl; -O-(C₁-C₄)alkyl-aryl; -S-(C₁-C₁₂)alkyl; -S-(C₂-C₁₂)alkenyl; -S(O)-(C₁-C₁₂)alkyl; -S(O)-(C₂-C₁₂)alkenyl; -S(O)₂-(C₁-C₁₂)alkyl; -S(O)₂-(C₂-C₁₂)alkenyl; a heterocycle comprising 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; a -(C₁-C₄)alkyl-heterocyclyl wherein the heterocyclyl of the -(C₁-C₄)alkyl-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; or a -O-heterocyclyl wherein the heterocyclyl of the -O-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N, O, or S, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups; further wherein the alkyl and alkenyl groups of -(C₁-C₁₂)alkyl, -(C₂-C₁₂)alkenyl, -(C₁-C₁₂)alkyl-O-(C₁-C₄)alkyl, -(C₁-C₁₂)alkyl-O-H, -(C₁-C₁₂)alkyl-O-(C₂-C₄)alkenyl, -(C₂-C₁₂)alkenyl-O-(C₁-C₄)alkyl, -(C₂-C₁₂)alkenyl-OH, -(C₂-C₁₂)alkenyl-O-(C₂-C₄)alkenyl, -O-(C₁-C₁₂)alkyl, -O-(C₂-C₁₂)alkenyl, and -O-(C₁-C₄)alkyl-aryl are

unsubstituted or are substituted with from 1 to 4 substituents selected from -F, -Cl, -OH, (=O), -NH₂, NH(C₁-C₄)alkyl, -N((C₁-C₄)alkyl)₂, aryl, unsubstituted -(C₁-C₂)alkyl, or unsubstituted -O-(C₁-C₂)alkyl;

X is O, S, or NR^a wherein R^a is selected from -H or -(C₁-C₆) alkyl groups;

W, Y, and Z are selected from N or CR¹³; wherein 0, 1, or 2 of W, Y, and Z is N; and further wherein Z is not N if R² is -F;

R¹ is selected from -H, -(C₁-C₆)alkyl, -(C₂-C₆)alkenyl, -(C₂-C₆)alkynyl, -(C₁-C₄)alkyl-O-(C₁-C₄)alkyl, heterocyclyl, aryl, or heteroaryl;

R^{1a} is selected from -H and -(C₁-C₄)alkyl;

or R¹ and R^{1a} may join together to form a 3 to 7 membered ring with 0, 1, or 2 heteroatoms selected from O, N, or S ;

R² is selected from -H, -F, -CF₃, or -O-(C₁-C₆)alkyl;

R³ is -H, -F, -Cl, -OH, -(C₁-C₄)alkyl, -O-(C₁-C₃)alkyl, or -S-(C₁-C₂)alkyl;

R⁷ and R⁸ are independently selected from -H and -(C₁-C₄)alkyl;

R⁹ and R¹⁰ are independently selected from -H and -(C₁-C₄)alkyl;

each of R^{11a}, R^{11b}, R^{11c}, and R^{11d} is independently selected from -H, -F, -Cl, -(C₁-C₄)alkyl, or -O-(C₁-C₄)alkyl; and R^{11a} is absent if G is N; R^{11b} is absent if J is N, R^{11c} is absent if L is N; or R^{11d} is absent if K is N;

each of R^{12a}, R^{12b}, and R^{12c} is independently selected from -H, -F, -Cl, -(C₁-C₄)alkyl, or -O-(C₁-C₄)alkyl;

R¹³ is selected from -H, -F, -(C₁-C₄)alkyl, and -O-(C₁-C₄)alkyl; and

q is 1 or 2.

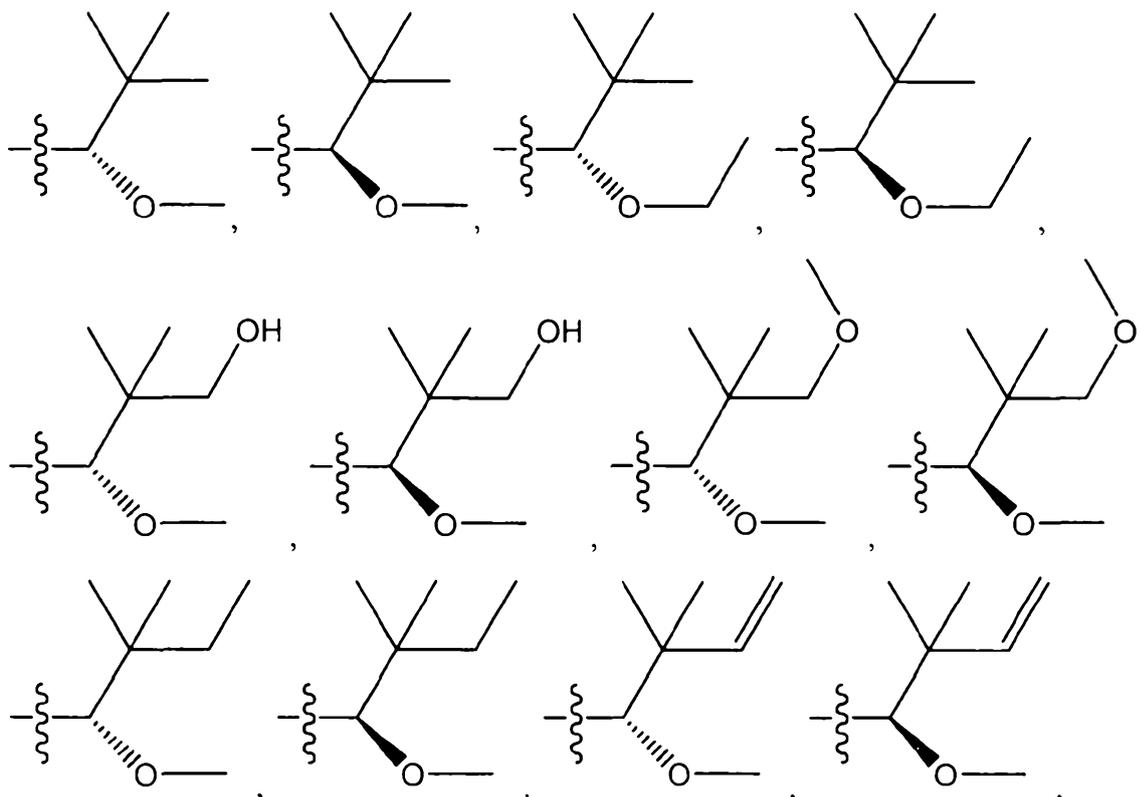
2. The compound of Claim 1, wherein R³ is selected from -F, -Cl, -OCHF₂, -OCH₂CF₃, -OCF₃, -O-cyclopropyl, -CF₃, or -CHF₂.

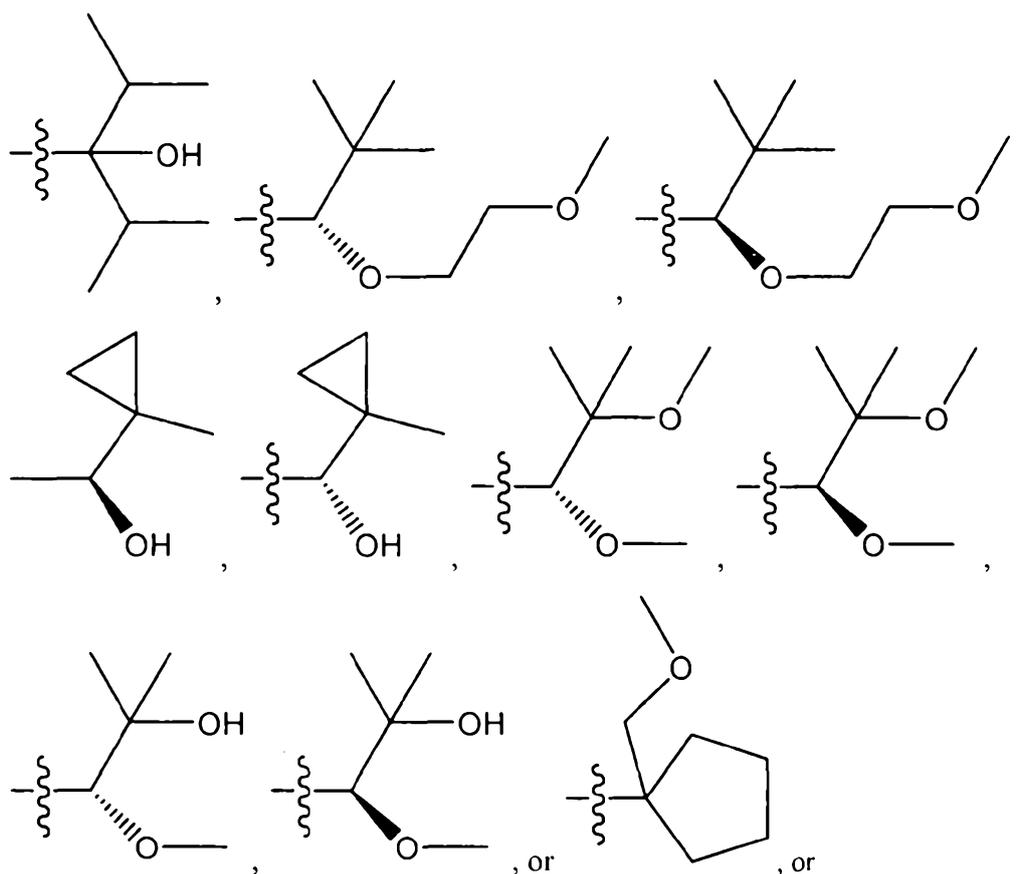
3. The compound of Claim 1 or Claim 2, wherein W and Z are C-H and Y is N.

4. The compound of any one of Claims 1-3, wherein A is selected from -(C₄-C₁₂)alkyl, -(C₄-C₁₂)alkenyl, -(C₃-C₁₂)alkyl-O-(C₁-C₄)alkyl, -(C₃-C₁₂)alkyl-OH, -(C₃-C₁₂)alkenyl-O-(C₁-C₄)alkyl, -(C₃-C₁₂)alkenyl-OH, -O-(C₄-C₁₂)alkyl, -O-(C₄-C₁₂)alkenyl, a heterocycle comprising 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N or O, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups, a -(C₁-C₄)alkyl-heterocyclyl wherein the heterocyclyl of the -(C₁-C₄)alkyl-heterocyclyl comprises 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N or O, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups, or a -O-heterocyclyl wherein the heterocyclyl of the -O-heterocyclyl comprises 4 to 7 ring

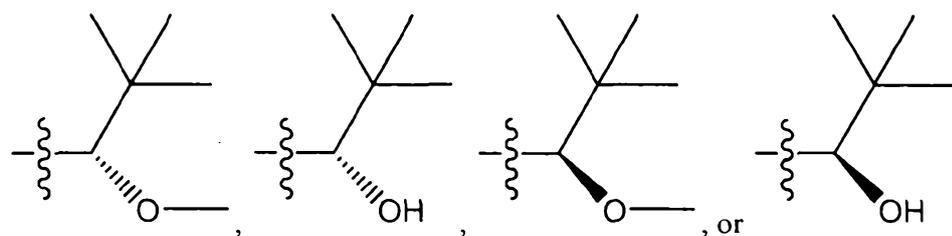
members of which 1 or 2 are heteroatoms selected from N or O, wherein the heterocycle has 0 or 1 double bond between ring members and is unsubstituted or is substituted with from 1 to 4 (C₁-C₂)alkyl groups, further wherein the alkyl and alkenyl groups of -(C₄-C₁₂)alkyl, -(C₄-C₁₂)alkenyl, -(C₃-C₁₂)alkyl-O-(C₁-C₄)alkyl, -(C₃-C₁₂)alkyl-O-H, -(C₃-C₁₂)alkenyl-O-(C₁-C₄)alkyl, -(C₃-C₁₂)alkenyl-OH, -O-(C₄-C₁₂)alkyl, or -O-(C₄-C₁₂)alkenyl are unsubstituted or are substituted with from 1 to 4 substituents selected from -F, -Cl, -OH, (=O), -NH₂, NH(C₁-C₄)alkyl, -N((C₁-C₄)alkyl)₂, aryl, unsubstituted -O-(C₁-C₂)alkyl, unsubstituted -(C₁-C₂)alkyl.

5. The compound of claim 4, wherein A is selected from -(C₄-C₁₂)alkyl, -(C₄-C₁₂)alkenyl, -(C₃-C₁₂)alkyl-O-(C₁-C₄)alkyl, -(C₃-C₁₂)alkyl-OH, -(C₃-C₁₂)alkenyl-O-(C₁-C₄)alkyl, -(C₃-C₁₂)alkenyl-OH, -O-(C₄-C₁₂)alkyl, or -O-(C₄-C₁₂)alkenyl, wherein the alkyl and alkenyl groups of -(C₄-C₁₂)alkyl, -(C₄-C₁₂)alkenyl, -(C₃-C₁₂)alkyl-O-(C₁-C₄)alkyl, -(C₃-C₁₂)alkyl-O-H, -(C₃-C₁₂)alkenyl-O-(C₁-C₄)alkyl, -(C₃-C₁₂)alkenyl-OH, -O-(C₄-C₁₂)alkyl, or -O-(C₄-C₁₂)alkenyl are unsubstituted or are substituted with from 1 to 4 substituents selected from -F, -Cl, -OH, (=O), -NH₂, NH(C₁-C₄)alkyl, or N((C₁-C₄)alkyl)₂, unsubstituted -O-(C₁-C₂)alkyl, or unsubstituted -(C₁-C₂)alkyl or wherein A is a -(C₄-C₈)alkyl-O-(C₁-C₂)alkyl, -(C₄-C₈)alkyl-OH, -(C₄-C₈)alkenyl-O-(C₁-C₂)alkyl, or -(C₄-C₈)alkenyl-OH and each of the alkyl and alkenyl groups of -(C₄-C₈)alkyl-O-(C₁-C₂)alkyl, -(C₄-C₈)alkyl-OH, -(C₄-C₈)alkenyl-O-(C₁-C₂)alkyl, or -(C₄-C₈)alkenyl-OH are unsubstituted or are substituted with 1 to 4 substituents selected from -OH, unsubstituted -O-(C₁-C₂)alkyl, or unsubstituted -(C₁-C₂)alkyl or wherein A is selected from

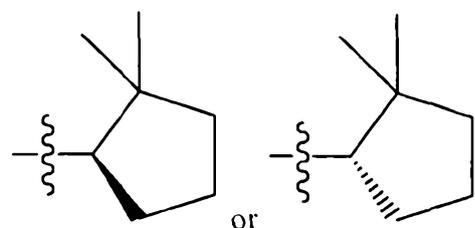




wherein A is



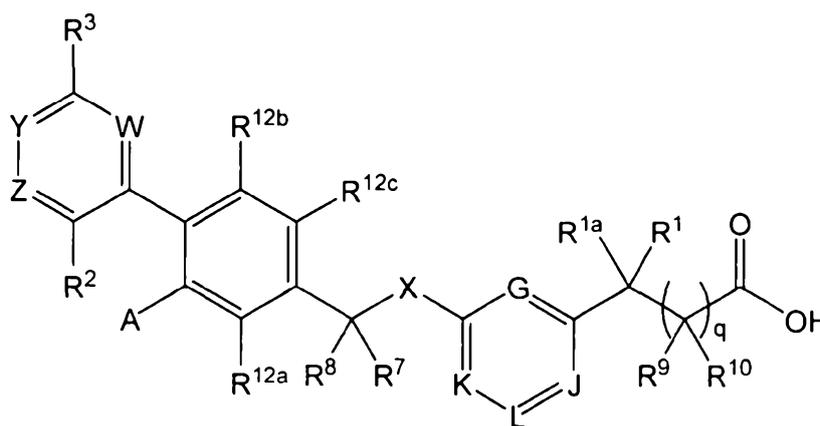
6. The compound of any one of Claims 1-3, wherein A is selected from



7. The compound of any one of Claims 1 to 6, wherein R¹ is a -CH₂-cyclopropyl, or a cyclopropyl or a cyclobutyl group that is optionally substituted with one or two methyl groups.

8. The compound of Claim 1, wherein K is N; G is CR^{11a}; J is CR^{11b}; and L is CR^{11c}.

9. The compound of Claim 1, wherein G is CR^{11a}; J is CR^{11b}; L is CR^{11c}; K is CR^{11d}; R^{11a} is H or F; R^{11b}, R^{11c}, and R^{11d} are H; R^{1a} is H; W is C-H; Z is C-H; R² is F; R³ is methoxy; R⁷ is H; R⁸ is H; R⁹ is H; R¹⁰ is H; X is O; q is 1; and two of R^{12a}, R^{12b}, and R^{12c} are H and the other of R^{12a}, R^{12b}, and R^{12c} is F.
10. The compound of any one of Claims 1-7, wherein R^{11a} is H, R^{11b} is H, R^{11c} is H, and R^{11d} is H.
11. The compound of Claim 10, wherein R^{12c} is H.
12. A compound of formula I:



I

or a pharmaceutically acceptable salt, stereoisomer, C₁-C₆ alkyl ester, or a mixture thereof, wherein

G is selected from N or CR^{11a};

J is selected from N or CR^{11b};

L is selected from N or CR^{11c};

K is selected from N or CR^{11d};

wherein 0 or 1 of G, J, L, and K is N;

A is selected from (C₁-C₁₂)alkyl, (C₂-C₁₂)alkenyl, -O-(C₁-C₁₂)alkyl, -O-(C₂-C₁₂)alkenyl, -O-(C₁-C₄)alkyl-aryl, or a heterocycle comprising 4 to 7 ring members of which 1 or 2 are heteroatoms selected from N or O, wherein the heterocycle has 0 or 1 double bond between ring members;

X is O or S;

W, Y, and Z are selected from N or CR¹³; wherein 0 or 1 of W, Y, and Z is N; and further wherein Z is not N if R² is F;

R¹ is selected from H, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, -(C₁-C₄)alkyl-O-(C₁-C₄)alkyl, heterocyclyl, aryl, or heteroaryl;

R^{1a} is selected from H and (C₁-C₄)alkyl;

R² is selected from H, F, CF₃, or (C₁-C₆)alkoxy;

R^3 is H, -OH, -O-(C₁-C₂)alkyl, or -S-(C₁-C₂)alkyl;

R^7 and R^8 are independently selected from H and (C₁-C₄)alkyl;

R^9 and R^{10} are independently selected from H and (C₁-C₄)alkyl;

Each of R^{11a} , R^{11b} , R^{11c} , and R^{11d} is independently selected from H, F, Cl, (C₁-C₄)alkyl, or (C₁-C₄)alkoxy; and R^{11a} is absent if G is N; R^{11b} is absent if J is N, R^{11c} is absent if L is N; or R^{11d} is absent if K is N;

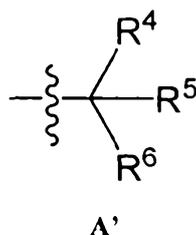
Each of R^{12a} , R^{12b} , and R^{12c} is independently selected from H, F, Cl, (C₁-C₄)alkyl, or (C₁-C₄)alkoxy;

R^{13} is selected from H, F, (C₁-C₄)alkyl, and -O-(C₁-C₄)alkyl; and

q is 1 or 2.

13. The compound of Claim 12, wherein each of R^{11a} , R^{11b} , R^{11c} , R^{11d} , R^{12a} , R^{12b} , and R^{12c} is H.
14. The compound of Claim 12 or Claim 13, wherein R^1 is a cyclopropyl or a cyclobutyl group that is optionally substituted.
15. The compound of Claim 12, wherein A is a branched chain (C₄-C₈)alkyl group.
16. The compound of Claim 15, wherein A is a t-butyl group.
17. The compound of Claim 12, wherein A is -O-(C₃-C₁₀)alkyl or -O-(C₃-C₁₀)alkenyl.
18. The compound of Claim 12, wherein G is CR^{11a}; J is CR^{11b}; L is CR^{11c}; K is CR^{11d}; R^{11a} , R^{11b} , R^{11c} , and R^{11d} are H; R^{1a} is H; W is C-H; Z is C-H; R^2 is F; R^3 is methoxy; R^7 is H; R^8 is H; R^9 is H; R^{10} is H; X is O; q is 1; and two of R^{12a} , R^{12b} , and R^{12c} are H and the other of R^{12a} , R^{12b} , and R^{12c} is F.
19. The compound of Claim 1 or Claim 12 wherein X is O.
20. The compound of any one of Claims 1 or 12 or 19, wherein G is CR^{11a}; J is CR^{11b}; L is CR^{11c}; and K is CR^{11d}.
21. The compound of any one of Claims 1, 12, 19 or 20, wherein R^3 is selected from -OH, -O(C₁-C₂)alkyl, or -S(C₁-C₂)alkyl.
22. The compound of Claim 21, wherein R^3 is methoxy.

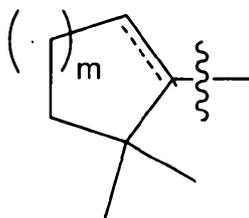
23. The compound of any one of Claims 1, 12, 19-21 or 22, wherein R^2 is selected from -F, -CF₃, or (C₁-C₆)alkoxy.
24. The compound of Claim 23, wherein R^2 is butoxy.
25. The compound of any one of Claims 1, 12, 19-21 or 22, wherein R^2 is H or F.
26. The compound of any one of Claims 1, 12, 19-24 or 25, wherein q is 1.
27. The compound of any one of Claims 1, 12, 19-25 or 26, wherein R^{1a} is H.
28. The compound of any one of Claims 1, 12, 19-26 or 27, wherein W, Y, and Z are all C-H.
29. The compound of any one of Claims 1, 12, 19-27 or 28, wherein A is selected from (C₃-C₁₀)alkyl or (C₄-C₁₀)alkenyl.
30. The compound of any one of Claims 1, 12, 19-27 or 28, wherein A is a group of formula A'



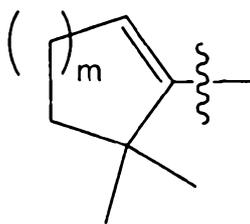
where the wavy line indicates the point of attachment; and

R^4 , R^5 , and R^6 are independently selected from H, F, (C₁-C₄)alkyl, wherein at least two of R^4 , R^5 , and R^6 are other than H; or two or three of R^4 , R^5 , and R^6 join together to form an optionally substituted saturated or partially unsaturated 3-8 membered monocyclic or bicyclic ring.

31. The compound of any one of Claims 1, 12, 19-27 or 28, wherein A is a (C₅-C₇)cycloalkyl group or a (C₅-C₇)cycloalkenyl group optionally substituted with 1, 2, 3, or 4 methyl groups; or wherein A has the formula

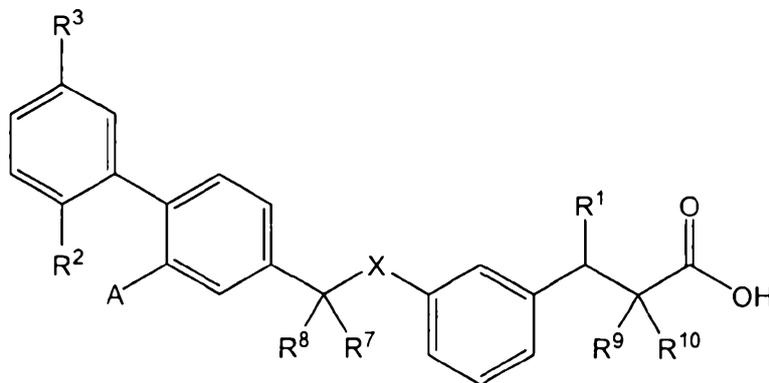


wherein m is 1, 2, or 3, and the dashed line indicates a single or double bond; or wherein A has the formula



wherein m is 1, 2, or 3.

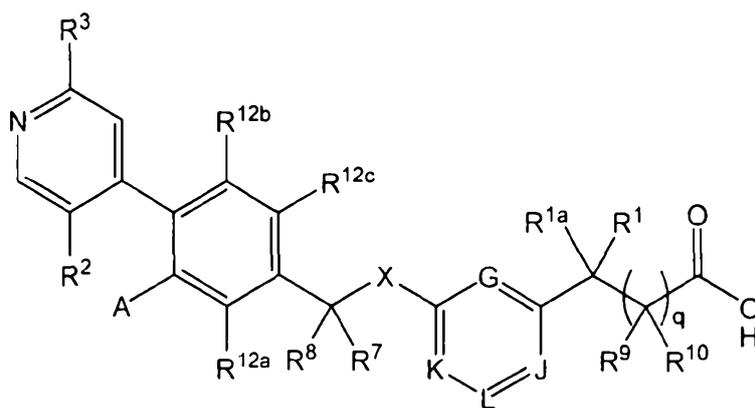
32. The compound of any one of Claims 1, 12, 19, 30 or 31, wherein R^7 and R^8 are both H.
33. The compound of any one of Claims 1, 12, 19-31 or 32, wherein R^9 and R^{10} are both H.
34. The compound of any one of Claims 1, 12, 19-32 or 33, wherein R^1 is a (C₁-C₄)alkyl or a (C₂-C₄)alkenyl.
35. The compound of Claim 1 or Claim 12, wherein G is CR^{11a}; J is CR^{11b}; L is CR^{11c}; K is CR^{11d}; R^{11a}, R^{11b}, R^{11c}, R^{11d}, R^{12a}, R^{12b}, and R^{12c} are all H; R^{1a} is H; W is C-H; Y, is C-H; Z is C-H; R² is F; R³ is methoxy; R⁷ is H; R⁸ is H; R⁹ is H; R¹⁰ is H; X is O, and q is 1.
36. The compound of Claim 1 or Claim 12, wherein the compound has the formula **II**



II

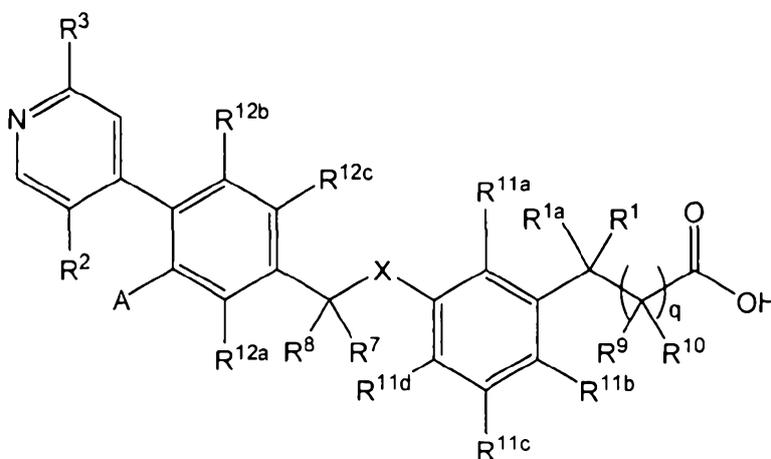
or a pharmaceutically acceptable salt, stereoisomer, C₁-C₆ alkyl ester, or a mixture thereof.

37. The compound of Claim 1 or Claim 12, wherein the compound has the formula **III**

**III**

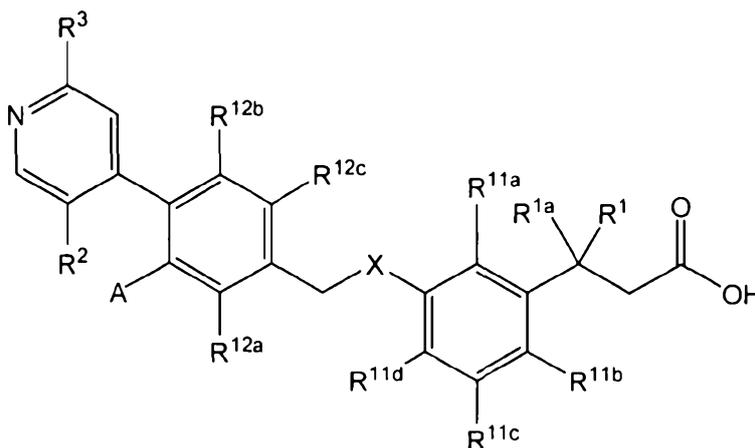
or a pharmaceutically acceptable salt, stereoisomer, C₁-C₆ alkyl ester, or a mixture thereof.

38. The compound of Claim 1 or Claim 12, wherein the compound has the formula **III'**

**III'**

or a pharmaceutically acceptable salt, stereoisomer, C₁-C₆ alkyl ester, or a mixture thereof.

39. The compound of Claim 1 or Claim 12, wherein the compound has the formula **III''**

**III''**

or a pharmaceutically acceptable salt, stereoisomer, C₁-C₆ alkyl ester, or a mixture thereof.

40. The compound of any one of Claims 1, 12, 19-34, 37, 38 or 39, wherein R^{11a} is F, R^{11b} is H, R^{11c} is H, and R^{11d} is H.
41. The compound of any one of Claims 1, 12, 19-34, 37-39 or 40, wherein R^{12c} is F.
42. The compound of any one of Claims 1, 12, 19-34, 37-40 or 41, wherein R^{12a} is H and R^{12b} is H.
43. The compound of any one of Claims 1-42, wherein the compound is a salt.
44. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier, diluent, or excipient, and the compound of any one of Claims 1-43.
45. The use of the compound of any one of Claims 1-43 in the preparation of a medicament for treating a disease or condition selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer and edema.
46. The use of claim 45 wherein the disease or condition is type II diabetes.
47. The use of the compound of any one of Claims 1-43 in the preparation of a medicament for increasing GLP-I levels in the blood plasma of a subject.
48. A method for treating a disease or condition, comprising: administering to a subject in need thereof, a therapeutically effective amount of the compound of any one of Claims 1-43, wherein the disease or condition is selected from the group consisting of type II diabetes, obesity, hyperglycemia, glucose intolerance, insulin resistance, hyperinsulinemia, hypercholesterolemia, hypertension, hyperlipoproteinemia, hyperlipidemia, hypertriglyceridemia, dyslipidemia, metabolic syndrome, syndrome X, cardiovascular disease, atherosclerosis, kidney disease, ketoacidosis, thrombotic disorders, nephropathy, diabetic neuropathy, diabetic retinopathy, sexual dysfunction, dermatopathy, dyspepsia, hypoglycemia, cancer, and edema.
49. The method of Claim 48, wherein the disease or condition is type II diabetes.

50. The method of Claim 48 or Claim 49, wherein the compound is administered in combination with a second therapeutic agent.
51. The method of Claim 50, wherein the second therapeutic agent is metformin, is a thiazolidinedione, or is a DPP-IV inhibitor.
52. A compound of Formula I; a pharmaceutical composition; a method of treating a disease or condition; use of the compound, substantially as herein described with reference to any one or more of the examples but excluding comparative examples.

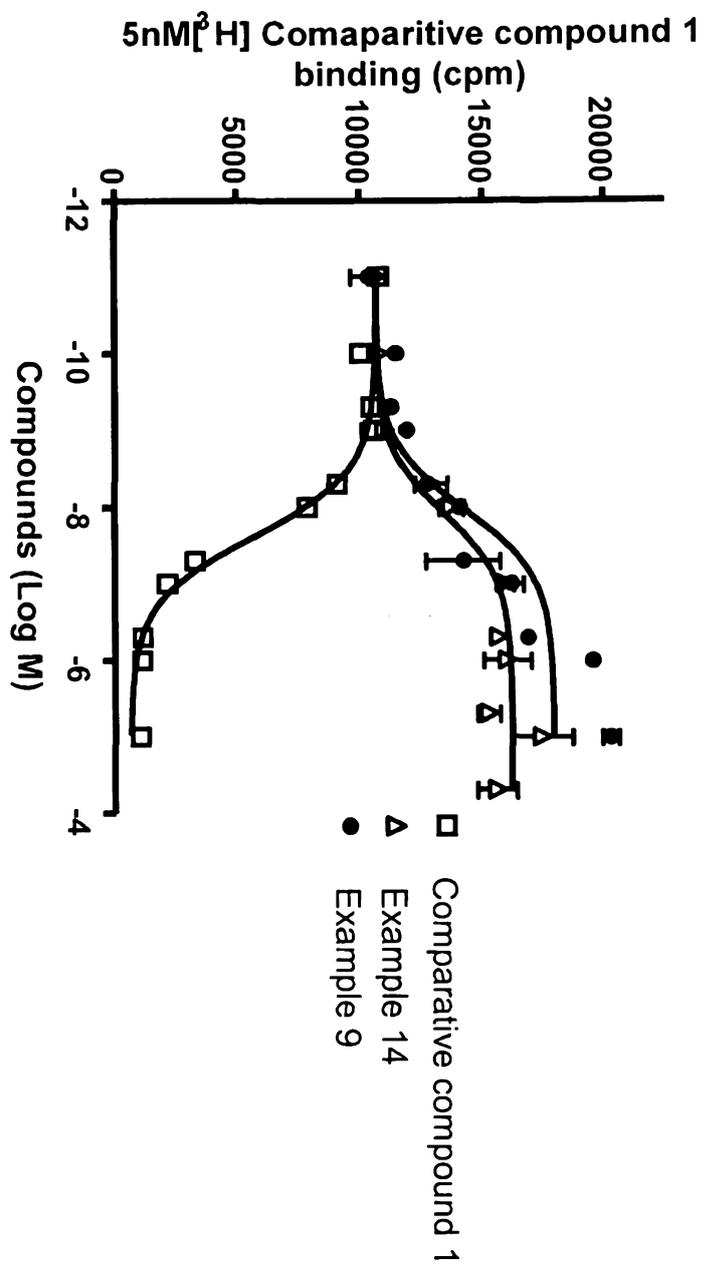


Figure 1

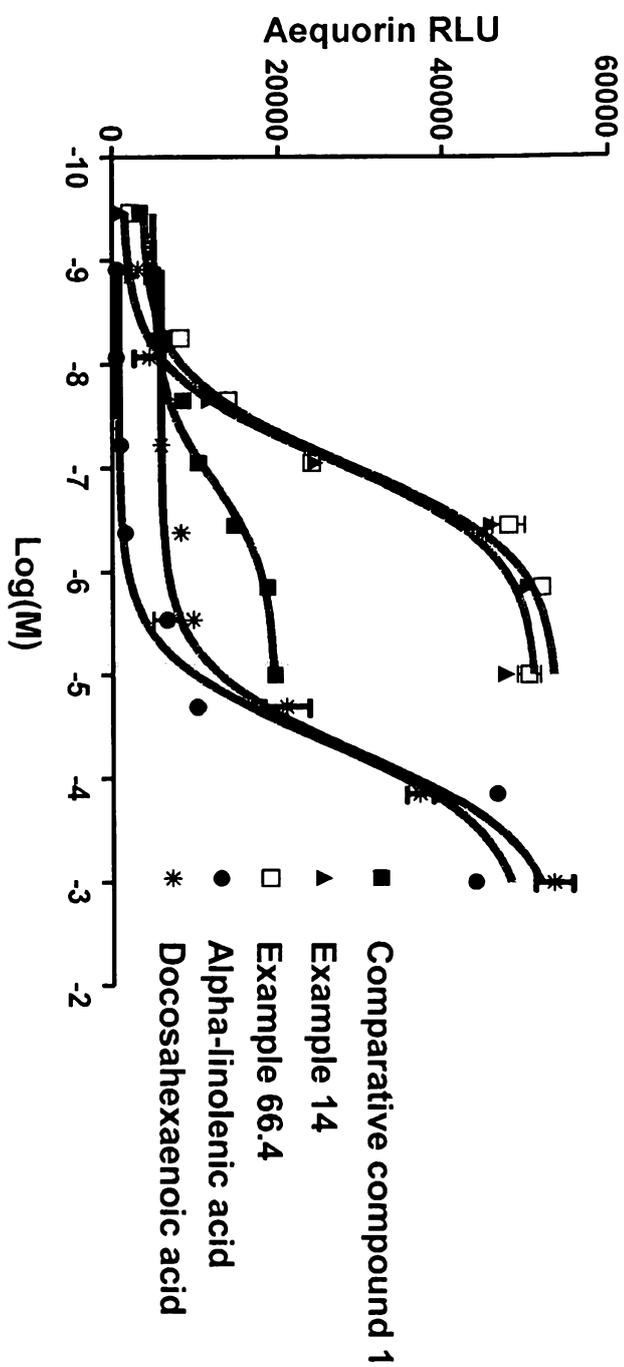


Figure 2

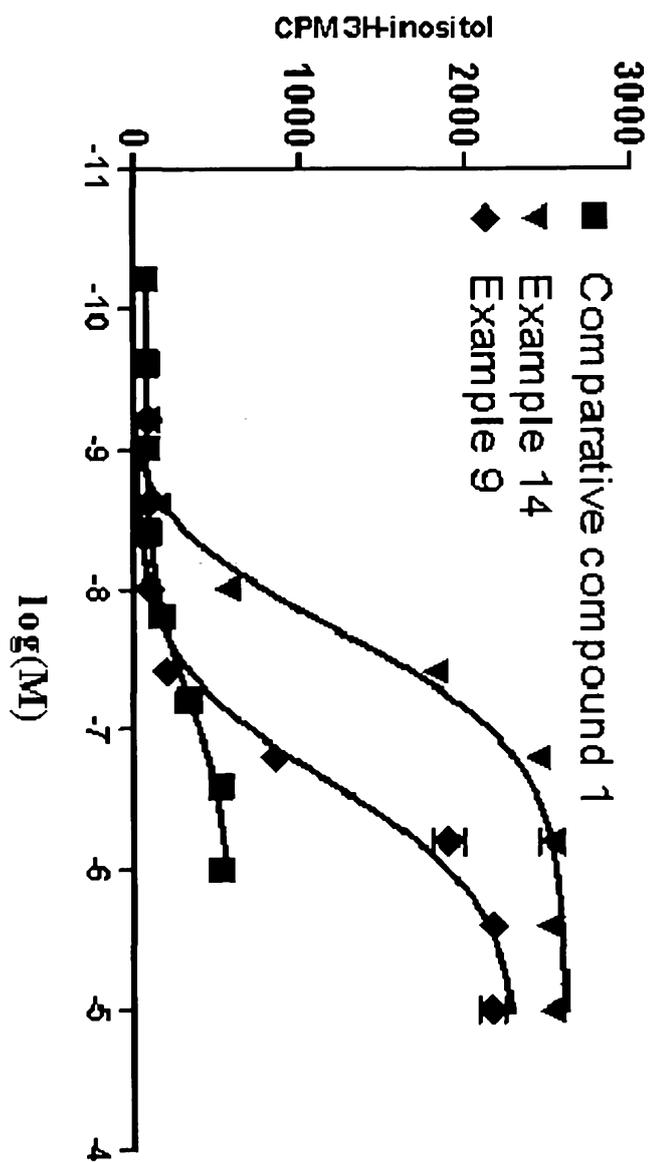


Figure 3

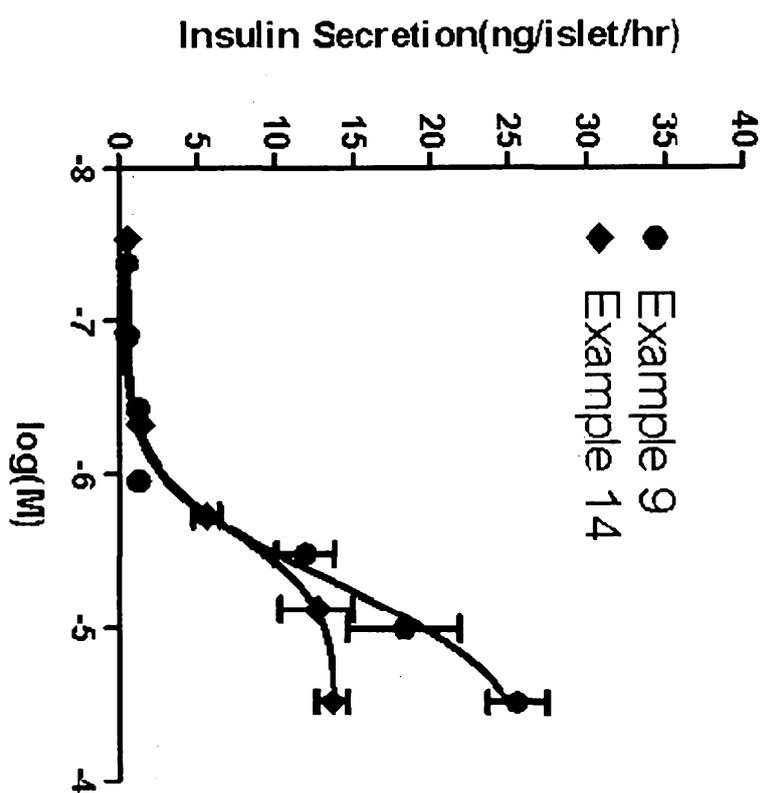


Figure 4

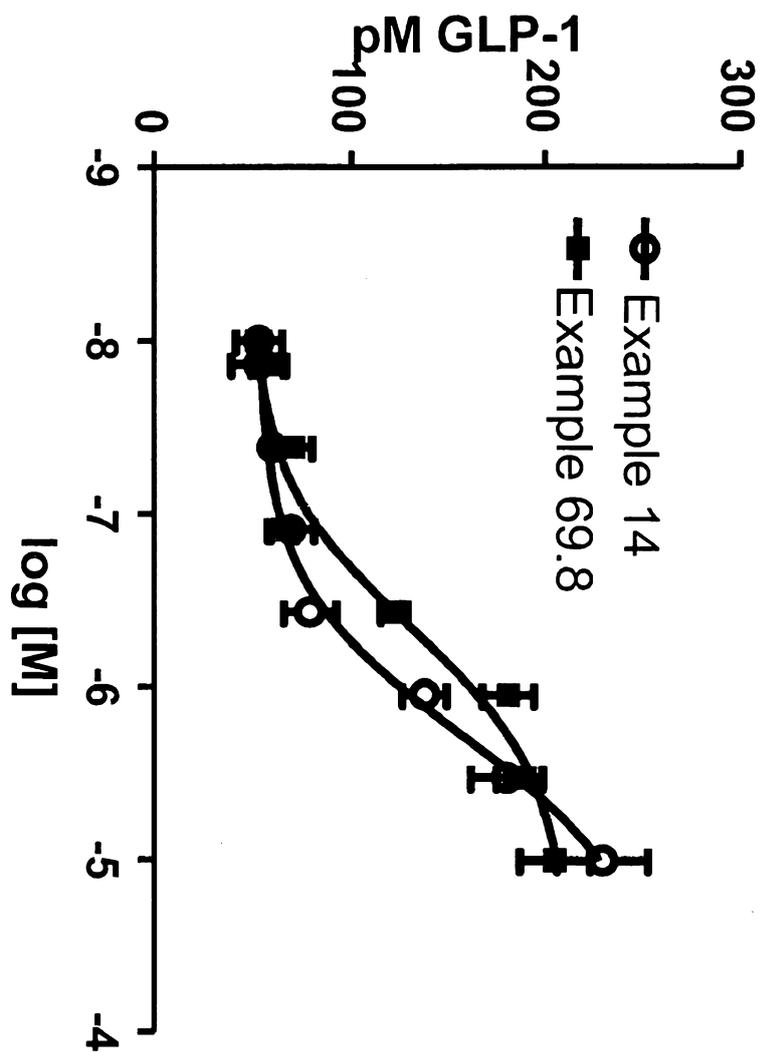


Figure 5

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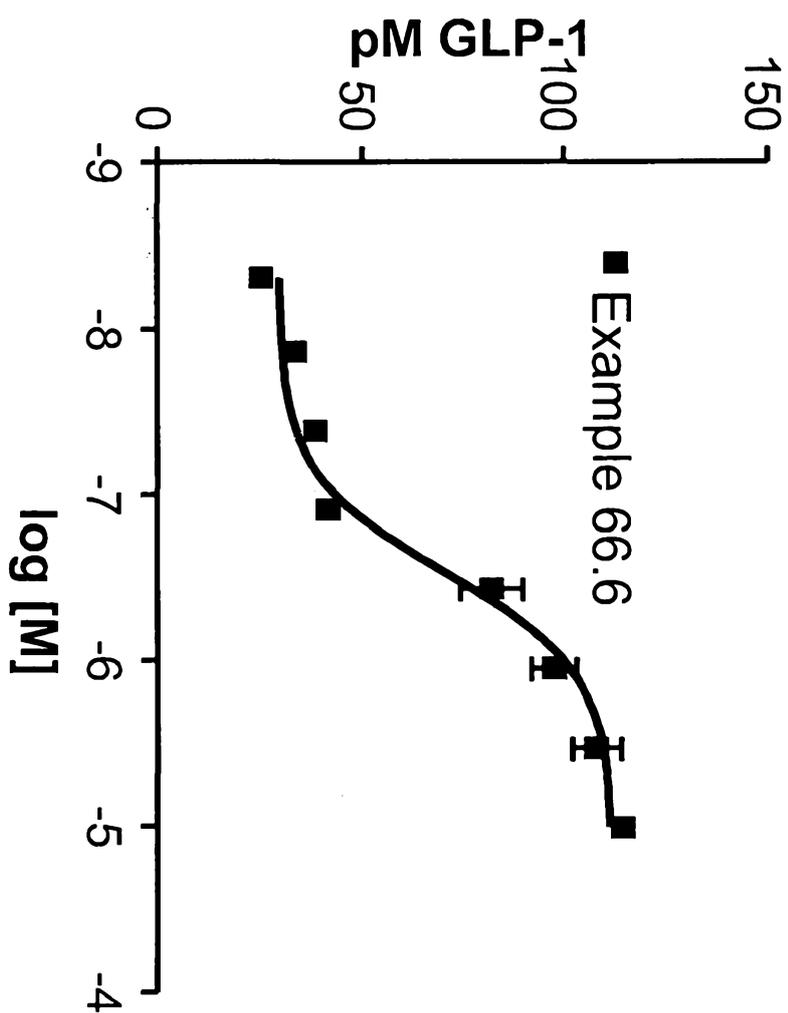


Figure 6

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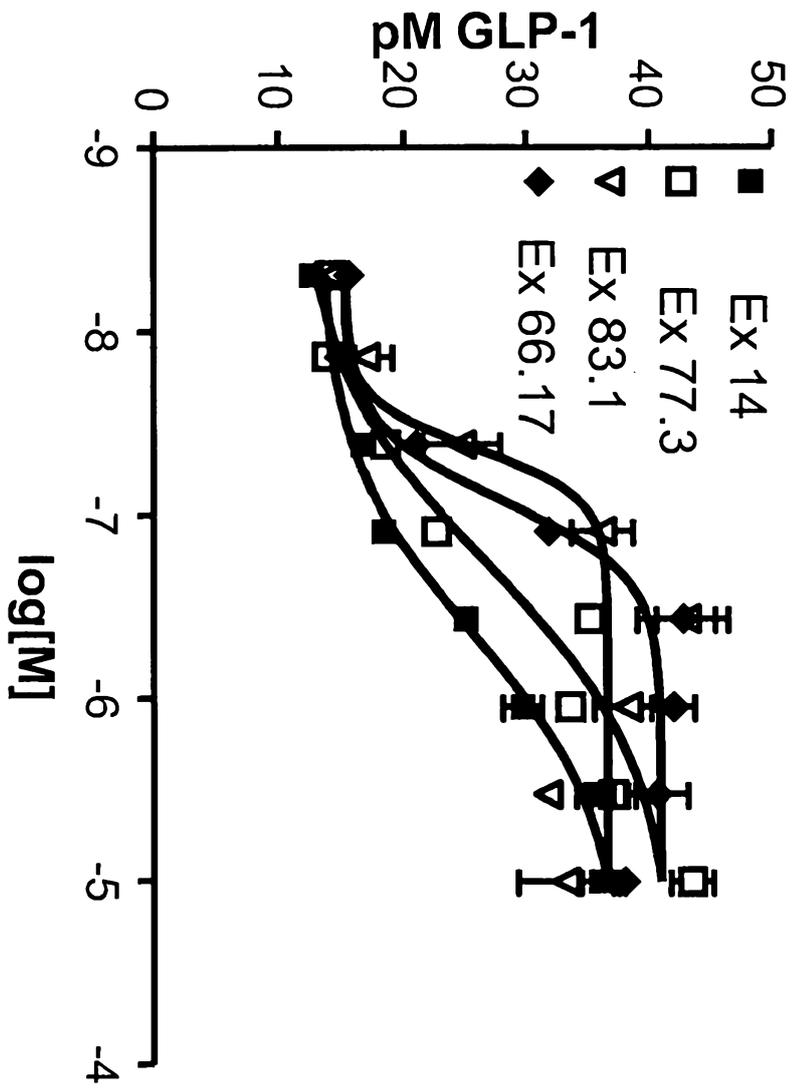


Figure 7

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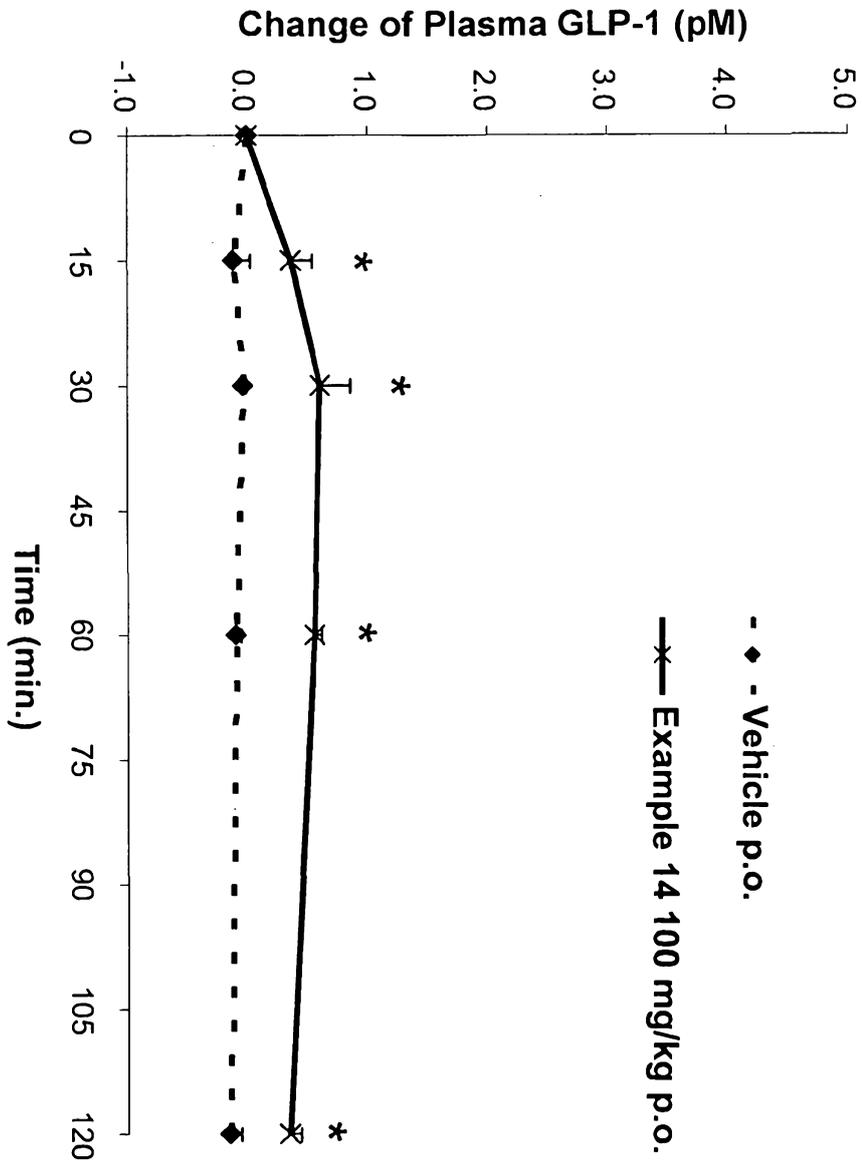


Figure 8

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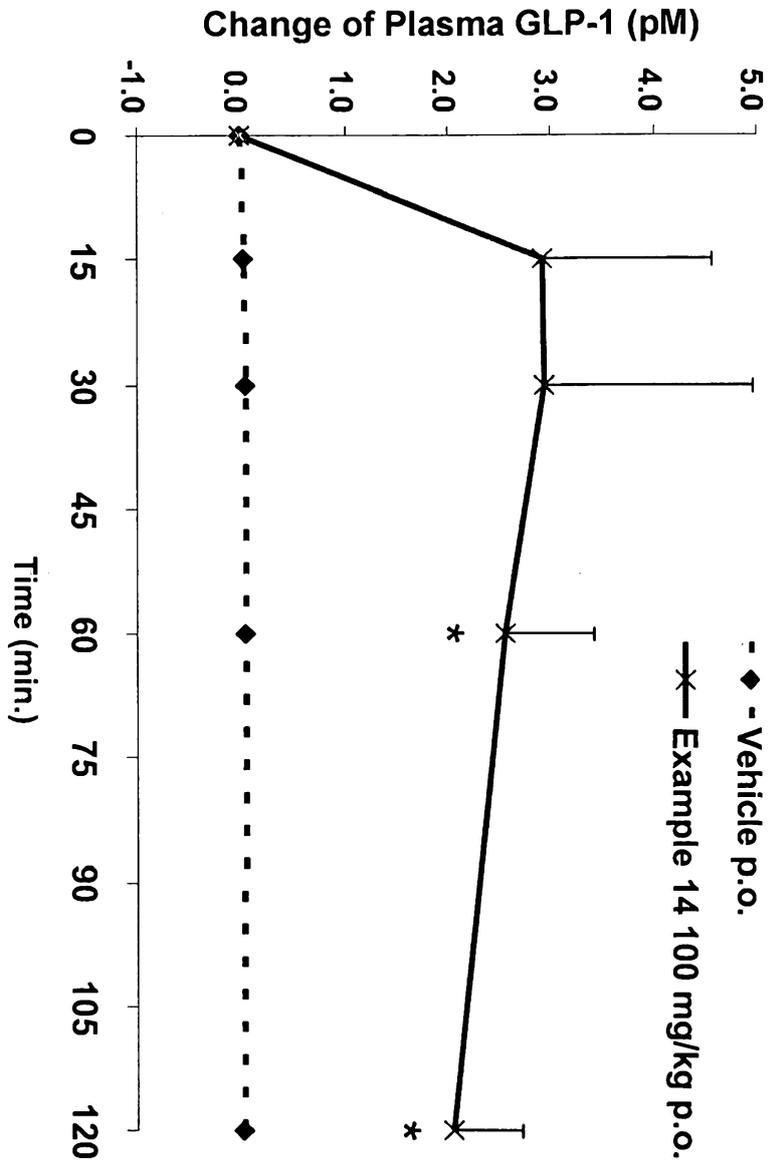


Figure 9

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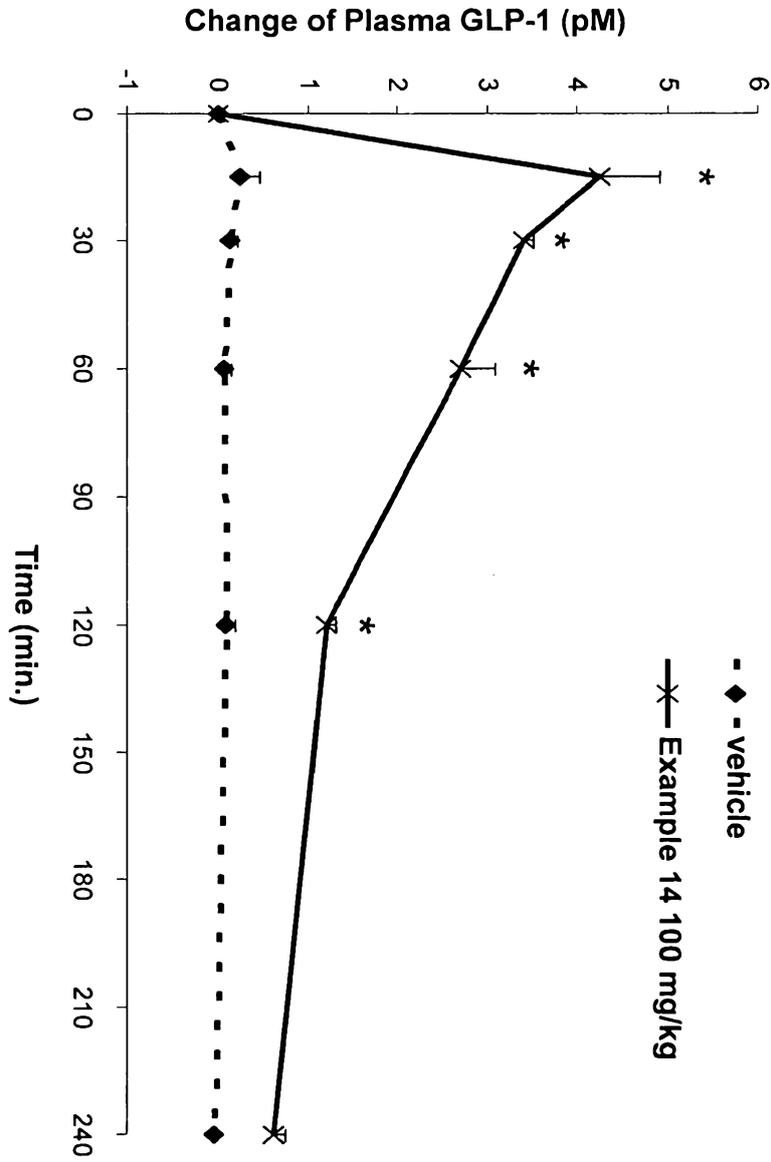


Figure 10

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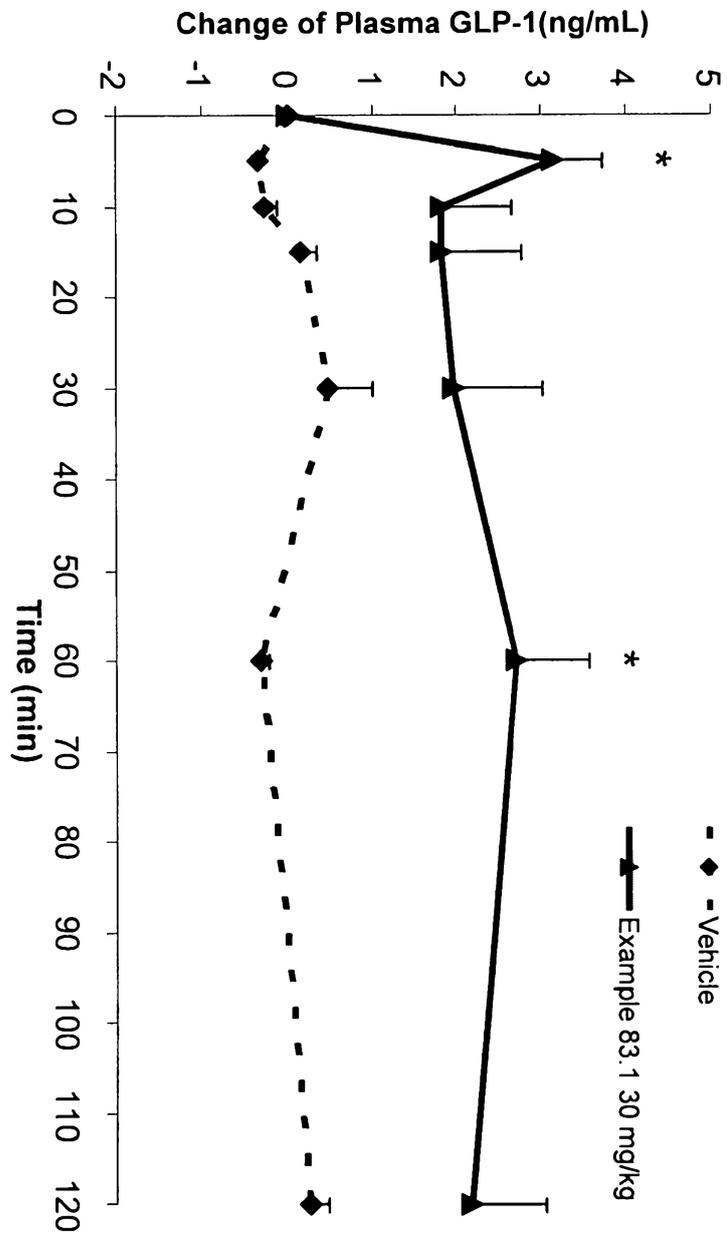


Figure 11